



# The Journal

OF THE

# American Medical Association

EDITED FOR THE ASSOCIATION UNDER THE DIRECTION OF THE BOARD OF TRUSTEES BY

MORRIS FISHBEIN, M.D.

VOLUME 116

JANUARY—JUNE 1941

AMERICAN MEDICAL ASSOCIATION, CHICAGO, 1941



# OFFICERS OF THE AMERICAN MEDICAL ASSOCIATION—1941-1942

HEADQUARTERS OF THE ASSOCIATION, 535 N. DEARBORN ST., CHICAGO

## GENERAL OFFICERS

PRESIDENT—FRANK H. LAHEY	Boston
PRESIDENT-ELECT—FRED W. RANKIN	Lexington, Ky.
VICE PRESIDENT—CHARLES A. DUKES	Oakland, Calif.
SECRETARY AND GENERAL MANAGER—OLIN WEST	Chicago
TREASURER—HERMAN L. KRETSCHMER	Chicago
SPEAKER, HOUSE OF DELEGATES—H. H. SHOULDERS	Nashville, Tenn.
VICE SPEAKER, HOUSE OF DELEGATES—R. W. FOUTS	Omaha
EDITOR—MORRIS FISHBEIN	Chicago
BUSINESS MANAGER—WILL C. BRAUN	Chicago

### BOARD OF TRUSTEES

Arthur W. Booth, Chairman, Elmira, N. Y., 1942  
R. L. Sensenich - South Bend, Ind., 1942  
Ernest E. Irons, Secretary - Chicago, 1943  
William F. Braasch - Rochester, Minn., 1943  
Roger I. Lee - Boston, 1944  
E. L. Henderson - Louisville, Ky., 1944  
Ralph A. Fenton - Portland, Ore., 1945  
James R. Bloss - Huntington, W. Va., 1945  
Charles W. Roberts - Atlanta, Ga., 1946

### JUDICIAL COUNCIL

Holman Taylor - Fort Worth, Texas, 1942  
John H. O'Shea - Spokane, Wash., 1943  
Edward R. Cuniffe - New York, 1944  
G. E. Follansbee, Chairman - Cleveland, 1945  
Walter F. Donaldson - Pittsburgh, 1946  
Olin West, Secretary, ex officio - Chicago

### COUNCIL ON MEDICAL EDUCATION AND HOSPITALS

Reginald Fitz - Boston, 1942  
Russell L. Haden - Cleveland, 1943  
Charles Gordon Heyd - New York, 1944  
H. G. Weiskotten - Syracuse, N. Y., 1945  
R. L. Wilbur, Chairman  
Stanford University, Calif., 1946  
John H. Musser - New Orleans, 1947  
Harvey B. Stone - Baltimore, 1948  
W. D. Cutter, Secretary - Chicago

### COUNCIL ON SCIENTIFIC ASSEMBLY

Clyde L. Cummer - Cleveland, 1942  
James E. Paullin, Chairman, Atlanta, Ga., 1943  
J. Gurney Taylor - Milwaukee, 1944  
A. A. Walker - Birmingham, Ala., 1945  
Frederick A. Collier - Ann Arbor, Mich., 1946

#### AND EX OFFICIO

The President-Elect, the Editor and the Secretary of the Association.

### COUNCIL ON PHARMACY AND CHEMISTRY

(Standing Committee of Board of Trustees)  
E. M. K. Geiling - Chicago, 1942  
W. W. Palmer - New York, 1942  
S. W. Clausen - Rochester, N. Y., 1942  
R. A. Hatcher - New York, 1943

\* Deceased.

Soma Weiss - Boston, 1943  
H. N. Cole - Cleveland, 1943  
Stuart Mudd - Philadelphia, 1943  
J. Howard Brown - Baltimore, 1944  
C. W. Edmunds - Ann Arbor, Mich., 1944  
David P. Barr - St. Louis, 1944  
Morris Fishbein - Chicago, 1945  
G. W. McCoy - New Orleans, 1945  
Perrin H. Long - Baltimore, 1945  
Elmer M. Nelson - Washington, D. C., 1945  
Torald Sollmann, Chairman - Cleveland, 1946  
W. C. Rose - Urbana, Ill., 1946  
E. L. Sevringhaus - Madison, Wis., 1946  
Theodore G. Klumpp, Secretary - Chicago

### COUNCIL ON PHYSICAL THERAPY

(Standing Committee of Board of Trustees)

Ralph Pemberton - Philadelphia, 1942  
Harry E. Mock, Chairman - Chicago, 1942  
Anthony C. Cipollaro - New York, 1942  
W. E. Garrey - Nashville, Tenn., 1943  
W. W. Coblentz - Washington, D. C., 1943  
John S. Coulter - Chicago, 1943  
Eben J. Carey - Milwaukee, 1944  
Frank R. Ober - Boston, 1944  
Frank D. Dickson - Kansas City, Mo., 1944  
A. U. Desjardins - Rochester, Minn., 1945  
H. B. Williams - New York, 1945  
Frank H. Krusen - Rochester, Minn., 1945  
Morris Fishbein, ex officio - Chicago  
Howard A. Carter, Secretary - Chicago

### COUNCIL ON FOODS AND NUTRITION

(Standing Committee of Board of Trustees)

Philip C. Jeans - Iowa City, 1942  
Mary Swartz Rose - New York, 1942  
Lydia J. Roberts - Chicago, 1943  
George R. Cowgill - New Haven, Conn., 1943  
C. S. Ladd - Bismarck, N. D., 1944  
Tom D. Spies - Cincinnati, 1944  
Irvine McQuarrie - Minneapolis, 1945  
Morris Fishbein - Chicago, 1945  
R. M. Wilder - Rochester, Minn., 1946  
Howard D. Lewis - Ann Arbor, Mich., 1946  
J. S. McLester, Chairman - Birmingham, Ala., 1946  
Franklin C. Bing, Secretary - Chicago

### COUNCIL ON INDUSTRIAL HEALTH

(Standing Committee of Board of Trustees)

Warren F. Draper - Washington, D. C., 1942  
Henry H. Kessler - Newark, N. J., 1942  
C. D. Selby - Detroit, 1942  
Raymond Hussey - Baltimore, 1942  
L. D. Bristol - New York, 1943  
C. W. Roberts - Atlanta, Ga., 1943  
Stanley J. Seeger, Chairman - Milwaukee, 1943  
Philip Drinker - Boston, 1943  
Harvey Bartle - Philadelphia, 1944  
Leroy U. Gardner - Saranac Lake, N. Y., 1944  
A. J. Lanza - New York, 1944  
Robert T. Legge - Berkeley, Calif., 1944  
C. M. Peterson, Secretary - Chicago

### COMMITTEE ON SCIENTIFIC EXHIBIT

Roger I. Lee, Chairman - Boston  
E. L. Henderson - Louisville, Ky.  
Ralph A. Fenton - Portland, Ore.  
Thomas G. Hull, Director - Chicago

### ADVISORY COMMITTEE

D. Chester Brown - Danbury, Conn.  
George Blumer - New Haven, Conn.  
Paul J. Hanzlik - San Francisco  
Ludvig Hektoen - Chicago  
Urban Maes - New Orleans  
Eben J. Carey - Milwaukee  
James P. Leake - Washington, D. C.

### BUREAU OF LEGAL MEDICINE AND LEGISLATION

J. W. Holloway Jr., Acting Director - Chicago

### BUREAU OF HEALTH EDUCATION

W. W. Bauer, Director - Chicago

### BUREAU OF INVESTIGATION

Paul C. Barton, Director - Chicago

### BUREAU OF MEDICAL ECONOMICS

R. G. Leland, Director - Chicago

### LIBRARY

Marjorie Hutchins Moore, Librarian - Chicago

## SECTION OFFICERS

PRACTICE OF MEDICINE—Chairman, Roy W. Scott, Cleveland; Vice Chairman, G. K. Fenn, Chicago; Secretary, W. D. Stroud, 1011 Clinton Street, Philadelphia.

SURGERY, GENERAL AND ABDOMINAL—Chairman, Arthur W. Allen, Boston; Vice Chairman, William L. Estes Jr., Bethlehem, Pa.; Secretary, Alton Ochsner, 1430 Tulane Avenue, New Orleans.

OBSTETRICS AND GYNECOLOGY—Chairman, Walter T. Dannreuther, New York; Vice Chairman, Leroy A. Calkins, Kansas City, Mo.; Secretary, Philip F. Williams, 2206 Locust Street, Philadelphia.

OPHTHALMOLOGY—Chairman, Lawrence T. Post, St. Louis; Vice Chairman, W. R. Buffington, New Orleans; Secretary, Derrick Vail, 441 Vine Street, Cincinnati.

LARYNGOLOGY, OTOTOLOGY AND RHINOLOGY—Chairman, Gordon F. Harkness, Davenport, Iowa; Vice Chairman, Daniel S. Cunnning, New York; Secretary, Louis H. Clerf, 1530 Locust Street, Philadelphia.

PEDIATRICS—Chairman, Philip M. Stimson, New York; Vice Chairman, Oscar Reiss, Los Angeles; Secretary, Hugh L. Dwyer, 315 Alameda Road, Kansas City, Mo.

EXPERIMENTAL MEDICINE AND THERAPEUTICS—Chairman, Wallace M. Yater, Washington, D. C.; Vice Chairman, Tinsley R. Harrison, Winston-Salem, N. C.; Secretary, Edgar V. Allen, 102 Second Avenue S.W., Rochester, Minn.

PATHOLOGY AND PHYSIOLOGY—Chairman, J. P. Simonds, Chicago; Vice Chairman, Frank C. Mann, Rochester, Minn.; Secretary, J. J. Moore, 55 East Washington Street, Chicago.

NERVOUS AND MENTAL DISEASES—Chairman, Stanley Cobb, Boston; Vice Chairman, A. R. Vonderahe, Cincinnati; Secretary, J. M. Nielsen, 727 West Seventh Street, Los Angeles.

DERMATOLOGY AND SYPHILOLOGY—Chairman, C. F. Lehmann, San Antonio, Texas; Vice Chairman, Paul E. Bechet, New York; Secretary, Nelson P. Anderson, 2807 Wilshire Boulevard, Los Angeles.

PREVENTIVE AND INDUSTRIAL MEDICINE AND PUBLIC HEALTH—Chairman, Haven Emerson, New York; Vice Chairman, Joseph W. Mountin, Washington, D. C.; Secretary, W. A. Sawyer, 343 State Street, Rochester, N. Y.

UROLOGY—Chairman, Vincent J. O'Connor, Chicago; Vice Chairman, Gershon J. Thompson, Rochester, Minn.; Secretary, Grayson L. Carroll, 539 North Grand Boulevard, St. Louis.

ORTHOPEDIC SURGERY—Chairman, James A. Dickson, Cleveland; Vice Chairman, Guy A. Caldwell, New Orleans; Secretary, Francis M. McKeever, 1136 West Sixth Street, Los Angeles.

GASTROENTEROLOGY AND PROCTOLOGY—Chairman, Walter L. Palmer, Chicago; Vice Chairman, H. Terrell, Richmond, Va.; Secretary, S. J. ... 1th Avenue, Boston.

RADIOLOGY—Ralph S. Bromer, Bryn Mawr, Pa.; Vice Chairman, Lyell C. Kinney, San Diego, Calif.; Secretary, John T. Murphy, 421 Michigan Street, Toledo, Ohio.

ANESTHESIOLOGY—Chairman, T. J. Collier, Atlanta, Ga.; Vice Chairman, F. E. Hubbard, Montclair, N. J.; Secretary, John S. Lundy, 102 Second Avenue S.W., Rochester, Minn.

# The Journal of the American Medical Association

Published Under the Auspices of the Board of Trustees

VOL. 116, No. 1

COPYRIGHT, 1940, BY AMERICAN MEDICAL ASSOCIATION  
CHICAGO, ILLINOIS

JANUARY 4, 1941

## UNILATERAL EXOPHTHALMOS

E. C. ELLETT, M.D.

MEMPHIS, TENN.

Exophthalmos or proptosis is usually considered, and rightly so, to be due to something in the orbit pushing the eye forward. Only a careless observer would confuse the different conditions in which the eye itself is enlarged, e. g. buphthalmos, with the protrusion of a normal eye, or at least a normal sized eye, in advance of its normal or natural position. The "something," i. e. the cause of the exophthalmos, may be one of a variety of things, and some of them and what is best to do for them will be briefly considered.

Instruments to measure the protrusion have been devised, so that one does not have to depend on the sense of sight or touch to know when an eye protrudes beyond its fellow. The best known instrument is the Hertel exophthalmometer, a satisfactory instrument though somewhat difficult to use. It must be carefully applied to the outer orbital rim and kept in the same position on each side to give a perfect reading. A simpler instrument is the transparent one devised by Luedde, but since the position of the two eyes is not measured at the same time it requires great care to be sure that the instrument is similarly placed on each side in turn. The normal reading with the Hertel instrument seems to be about 15 mm., but it is variable.

The character of the protrusion differs with different causes. With some conditions that cause a general overfilling of the orbit by a general increase in its contents the eye projects straight forward and moves fairly well in every direction. This is the condition seen, for instance, in exophthalmic goiter. A tumor within the muscle cone, if not too large, produces the same effect, but a large tumor in the cone tends to move and displaces the eyeball to the side. Other tumors in the orbit, i. e. outside the muscle cone, push the eye to one side. It is astonishing to what extent an eye can be displaced without causing diplopia, even when the vision is normal and binocular vision unimpaired.

### EXOPHTHALMIC GOITER

There is no occasion to discuss here the nature of exophthalmic goiter, especially since it is not known why, or exactly how, hyperthyroidism causes exophthalmos, and nothing at all is known as to why it sometimes produces unilateral exophthalmos. The treatment is, in the first place, the treatment of hyperthyroidism, which may be medical or surgical according to circum-

stances, but the one symptom of proptosis may determine the nature as it does the urgency of the treatment. There are two operations which might be done on the eye, in case the condition is extreme or persistent and is not cared for by a protective bandage: One of these is tarsorrhaphy and the other is the orbital decompression operation devised by Naffziger, which consists in the removal of more or less of the roof of the orbit and sometimes the roof of the optic canal as well. This is not an operation for the ophthalmic surgeon, but it and the operation for the relief of the hyperthyroidism as well may find their chief indication in the exophthalmos and the danger to the eye which it involves.

Cases may be cited to illustrate this condition, in one of which the thyroid disturbance was not manifest for a long time after the proptosis, a not unusual condition:

CASE 1.—Mrs. L. C. G., aged 23, complained of protrusion of the left eye in 1935. In May 1936 the neck was swollen and the exophthalmometer measured 12 and 19 mm. The eye was otherwise normal, vision was 6/6 and the patient was able to read Jaeger's test type 1. She had been advised that she had a tumor and that the eye should be removed. If this statement was correct, the condition had apparently been considered an orbital tumor and exenteration of the orbit was considered. The basal metabolism was +16. An operation for goiter in June arrested the progress of the exophthalmos and relieved her of nervousness and other symptoms of hyperthyroidism. In October 1939 she was seen for an acute exudative choroiditis in the left eye, the condition being otherwise unchanged (fig. 1).

CASE 2.—V. L., a man aged 27, complained in 1933 of exophthalmos of the left eye of two months' duration. The vision, eyeground, nose, throat and sinuses were normal. The general physical examination was negative and the metabolic rate was normal. The exophthalmometer measured 15 and 20 mm. The orbit was explored from in front and some adventitious tissue was removed from within the muscle cone. It was reported to be an "epithelial-like medullary tumor, infiltrating the orbital fat." There was no change in the eye, and the patient was referred to a neurologic surgeon, Dr. R. E. Semmes, for an orbital decompression. No tumor was found at operation, but the extra-ocular muscles were hypertrophied, as has been found by Naffziger in such cases. The operation was followed by paralysis of the superior rectus muscle. In January 1935 the patient showed symptoms of hyperthyroidism, with a metabolic rate of +46 and a very rapid pulse. A subtotal thyroidectomy relieved these symptoms, but the eye is unchanged in 1940 (fig. 2).

### ORBITAL TUMOR

A tumor almost anywhere in the orbit causes the eye to protrude, because the only direction in which it can move is forward. If the tumor is directly behind the eye, i. e. in the muscle cone, it will push the eye directly forward, as has been mentioned. Such a tumor may grow so large that it protrudes to one side, and then the eye is displaced to the opposite side. Various motor disturbances and ulcerations of the cornea from exposure

Read before the Section on Ophthalmology at the Ninety-First Annual Session of the American Medical Association, New York, June 12, 1940. Owing to lack of space, this article is abbreviated in THE JOURNAL by the omission of part of the text and many of the illustrations. The complete article will appear in the Transactions of the Section and in the author's reprints.

insufficient without too much pressure on the eye the incision was carried around the rim of the orbit, and a temporary resection of the outer orbital wall was done. The tumor, consisting of three separate parts, was removed. The parts measured respectively 22 by 27 by 7 mm., 33 by 14 by 9 mm. and 10 by 16 by 6 mm. They were alike microscopically, all being small round cell sarcomas. Healing was uneventful. Vision was

itself reached from the floor of the nose to the floor of the cranial cavity and was about the same size from in front backward and laterally. It was considered inoperable. He was given roentgen and symptomatic therapy. The growth extended, the right optic nerve atrophied and the lenses showed some opacity, especially the left. He died in 1938, nine years after the first examination (fig. 20).

CASE 12.—J. I. I., a Negro man aged 79, complained that his left eye had been watering and red for a month and was getting worse. There was a firm swelling below the eye, lying beneath the whole lower lid, slightly elastic and apparently attached to the periosteum. Motion was limited, especially downward. The eyeball was normal but protruded. Vision was 6/7.5. The Wassermann reaction was negative. Roentgen examination was negative. There was no glandular involvement. The tear duct was not involved. Operation was advised but declined (fig. 21). The patient subsequently saw Dr. Thomas P. Mannigan, who informed me that a specimen was taken for biopsy and was reported as a granulomatous inflammation. The section suggested blastomycosis, but no fungi were found.

CASE 13.—J. W., a boy aged 12 years, gave the history that at the age of 1½ years the left eye turned in and protruded. This slowly increased and the vision failed. Vision in the normal right eye was 15/25 and in the left eye 3/200. A smooth, firm tumor filled the upper outer quadrant of the left orbit, pushing the eyeball so that it turned in and protruded. The eye was otherwise normal, but the fundus details were blurred. Under



Fig. 22.—Sebaceous cyst of the orbit of the left eye, before operation.

temporarily impaired and motion slowly returned. Six months later vision was 20/30; there was diplopia in the lower temporal field, poor outward motion and ptosis, and the fundus was normal. The patient lived nine years and had no local recurrence and no metastasis (figs. 16, 17 and 18).

CASE 10.—Mrs. B., aged 45, in 1913 had been subject to severe headaches for four years, and for about two years the right eye had been prominent. The projection was not very marked and the vision, eyeground and ocular movements were normal. There was nothing to be felt in the orbit, and the nose and sinuses were normal. In 1918 vision was 20/60 and the eye was more prominent. Figure 19 shows how she looked in 1920. Roentgenograms indicated an osteoma, but they were not at all good. In October 1920 she was admitted to the Touro Infirmary in New Orleans with a diagnosis of osteoma of the right temporofrontal region and orbit, complicated by panophthalmitis, acute nephritis and edema of the lungs. The eye was enucleated and three days later the patient became unconscious from uremic coma and died. This case was apparently one of hyperostosis rather than of osteoma, since osteoma originates in the sinuses. Leontiasis ossea can be excluded because it usually affects other bones than those of the orbit.

CASE 11.—W. K., a boy aged 15 years, a patient of Dr. W. W. Hatcher of Imboden, Ark., was seen in December 1929. The left eye had converged five or six years before and he had worn glasses, with a diagnosis of paralysis of the left external rectus muscle. Vision was said to be good at first and there was diplopia, but the vision gradually failed. There was headache over the left eye and the left eye protruded. The left nostril was obstructed. A large hard mass could be felt at the inner side of the orbit, and a hard smooth swelling could be seen in the left nostril. Vision was limited to ability to count fingers at 6 inches, owing to atrophy of the optic nerve. The exophthalmometer measured 14 mm. and 21 mm. A roentgenogram showed islands of bone in the tumor, and the growth



Fig. 26.—Hemangioma of the orbit of the left eye, before operation.

ether anesthesia a canthotomy was done and the tumor removed through an incision in the conjunctiva. The growth was a sebaceous cyst and lay outside the muscle cone and was not attached to the periosteum or muscles. The deformity, apparent in figure 23, was due to (1) the canthotomy, (2) enlargement of the bony orbit from pressure and (3) absorption of the orbital fat. The eye still turned in, and outward motion was defective (figs. 22 and 23). The last photograph of the patient (fig. 24) was taken fourteen years after the operation.

## VASCULAR TUMORS

Another type of tumor is the vascular tumor. The characteristics of these are slow growth, a bluish discoloration and the fact that nothing is usually to be felt in the orbit and that removal of part of the tumor seems effective in relieving the proptosis. These seem to me to be the most difficult cases in which to operate, because there is no difference in the consistency of the tumor and the orbital fat and connective tissues, so that they are not well defined; but the tumor consists of a series of spaces with connective tissue septums, and if they are ruptured and the blood escapes it is practically impossible to remove them satisfactorily. A feature of this type of tumor is that it is frequently congenital. The difficulties of performing the operation on a small child are great, and since the tumors are often stationary or of very slow growth it is feasible and advisable to defer surgery till the child is several years old. In the meantime roentgen or radium therapy should be tried, with considerable prospect of a good result. The technical difficulty of operation in such cases has been mentioned. If some safe method of coagulating the blood in an angioma in this situation could be found it would make the operation very easy, but one hesitates to introduce coagulating fluids into a tumor which probably communicates freely with the intracranial sinuses and which cannot be surely cut off by ligature or otherwise from its deep connections.

CASE 14.—Mrs. S. was first seen when she was a girl of 15, in 1911. At the age of 9 years the left eye had protruded for a while and then receded to an almost normal position until three months before her visit, when it again protruded. There was constant pain, diplopia and protrusion of the eye. The vision and eyeground were normal but the tissue of the orbit had a cystic feel in the upper and outer angle. The nose and sinuses were normal. The patient was not seen again for nine years, when there was a soft blue tumor visible in the upper and outer portion of the left orbit. It did not pulsate, but the eye now protruded 14 mm. beyond the fellow eye. The eyeground and vision were normal, so it was decided to attempt to remove the tumor without disturbing the eye. Exposure through the conjunctiva and muscle did not give sufficient room, so a temporary resection of the external wall of the orbit was done. Through this opening the larger part of the tumor was removed, but not all of it could be reached, as it extended to the apex of the orbit; nor could it be readily differentiated from the other orbital tissues, and removal of the eye was not intended. After two years the vision was normal and the eye protruded 5 mm. (figs. 25, 26 and 27).

The pathologic report was not satisfactory. Either the specimen was mixed with some other in the laboratory or the examination was made of some other part of the mass than the tumor itself. Clinically the growth was a cavernous angioma.

CASE 15.—L. W., a girl aged 13 years, was seen in 1934. The left eye had been protruding for four years. The nose and sinuses were normal. In the orbit a soft mass could be felt down and in. The exophthalmometer measured 13 and 26 mm.; vision was normal. Exploration of the orbit from in front,



Fig. 29.—Hemangioma of the orbit of the left eye, before operation.

down and in, on May 13, 1937, gave negative results. On May 21 Dr. Semmes explored the orbit from above and thought that he found and coagulated a small angioma at the apex of the orbit. This operation was followed by ptosis and slight lessening of the exophthalmos. In February 1938 a firm mass could be felt down and in, and the lid over this location was discolored (bluish). Under ether anesthesia this was exposed by a conjunctival incision and a firm dark mass was dissected out. The pathologic report was cavernous hemangioma. The motion of the eye is now limited, the nerve is pale and the field is much contracted up and in. Vision is 6/6 with glasses, the right pupil measures 5 mm. and is active and the left 7 mm. and feebly active. The vessels are normal (figs. 28, 29 and 30).

## PSEUDOTUMOR

A curious group is that described as pseudotumor, illustrated by the following cases:

CASE 16.—Mrs. M. I., aged 45, was seen in August 1939 complaining of sudden failure of vision and protrusion of the right eye of two weeks' duration. Significant points in her history were a severe right-sided pain in the face following the extraction of a tooth and a right-sided deafness in April 1939 which lasted a month. No explanation was found for either of these events. The present illness began with pain in the right side of the face. Examination showed a normal left eye and a protruding right eye, paralysis of the sixth and paresis of the third and fourth cranial nerves on the right side. The pupil reacted feebly, consensual action being better than direct. The fundus was essentially normal. The impression was that of an aneurysm or tumor. The patient went to Baltimore; Dr. Dandy furnished the subsequent history. He was suspicious of aneurysm but operated on account of increasing pain. There was no tumor seen intracranially and the orbital roof was removed. When the orbital capsule was split, a large amount of orbital fat protruded and some was removed. A hard small round nodule was found at the apex of the orbit, fixed and lying beneath the optic nerve. It was removed and found to be composed of chronic inflammatory tissue.

The diagnosis was pseudotumor.

The photographs reproduced in figures 31 and 32 were taken nearly a year after the operation. There was then no apparent exophthalmos but optic nerve atrophy and paralysis of the right third nerve.

CASE 17.—H. P., a man aged 63, said that following a trifling injury to the left eye in 1938 he lost his vision and a year later the eye began to swell. When seen in April 1940 the left eye protruded and was painful. The exophthalmometer reading was 10 and 22 mm., and there was a swelling of the left temporal region, as shown in his photograph. Motion was limited in all directions. The nose was open but a roentgenogram showed that the left antrum, sphenoid and ethmoids were cloudy and there was an erosion of the external wall of the orbit. The nerve was white, the vessels were normal, the eye was blind and tension was normal. Nothing could be felt in the orbit. It seemed that an infiltrating growth was present, invading the orbit and adjacent sinuses and breaking through into the zygomatic fossa. Roentgen treatments seem to be reducing the size of the mass and have relieved the pain, which was a prominent symptom (fig. 33).



Fig. 36.—Schüller-Christian's disease (unilateral exophthalmos) of the right eye.

## GENERAL DISEASE AS CAUSE

Certain general diseases can cause unilateral exophthalmos and should be borne in mind by the ophthalmologist. Two of these are chloroma and xanthomatosis. I cannot show a picture of the former but can of one

of the forms of xanthomatosis, namely Schüller-Christian's disease. It is due to a disturbance of lipid metabolism with a deposit of lipoids in the tissue, the characteristic lesions being in the bones, as may be seen in roentgenograms. The significant signs of this condition are exophthalmos, large defects in the bones of the skull, and diabetes insipidus. The optic nerve and retina may be involved, with impairment of sight. The sight may also suffer from exposure of the cornea. Another related form is mentioned by Knapp<sup>4</sup> as a tumor of the orbit arising from the frontal bones which (1) forms a tumor below the upper bony margin of the orbit, causing exophthalmos, (2) causes a defect in the frontal bone, (3) presents certain histologic peculiarities, (4) has slow growth and (5) is benignant. This is very different from such forms of xanthomatosis as Schüller-Christian's disease. Roentgen treatment is about all that



Fig. 42.—Unilateral exophthalmos of the left eye of unknown origin.

can be done, and the child whose case I report seemed to improve and was symptomatically well when she died:

CASE 20.—Mary J. H., aged 6 years, was seen in September 1936. Two years previously she had aching joints, because of which her tonsils were removed. For three months the right eye had protruded, and at times there was a discoloration around the orbital region. A nodular mass could be felt in the orbit, down and out. Motion and vision were normal. A swelling of the disk, thought to be pseudoneuritis, was present in both eyes. The exophthalmometer measured 25 and 15 mm. The general physical examination was entirely negative, but roentgenograms showed patches characteristic of xanthomatosis. These lesions, together with flabby muscles, especially the masseters, were the basis of the diagnosis of Schüller-Christian's disease. This is due to disturbed lipid metabolism. The deposit in the skull and long bones resembled osteomyelitis. The exophthalmos, the lipid deposits in the bones and the diabetes insipidus are the usual diagnostic signs of Schüller-Christian's disease (figs. 36, 37, 38 and 39).

The blood showed 82 per cent hemoglobin, nearly 4,000,000 red cells and 8,000 white cells, with 45 per cent polymorpho-

nuclear leukocytes, 49 per cent small lymphocytes, 3 per cent transitional forms, and 3 per cent eosinophils. Roentgen treatment caused marked improvement, especially in the exophthalmos, which receded to 15 mm., and in general strength, but the child died a few months later.

#### INTERMITTENT EXOPHTHALMOS

The following is one of the unusual cases of intermittent exophthalmos:

CASE 21.—C. D., a man aged 51, a patient of Dr. T. C. Chapman of Brownsville, Tenn., had for twenty years noticed when he stooped, when he had a cold or when he had on a tight collar that the left eye protruded. Vision in each eye was 6/20 and with proper glasses it was 6/6 and the patient was able to read Jaeger's test type 1. Both eyes when at rest were normal inside and out. Pressure on the right angular vein had no effect, but pressure on the left one caused protrusion of the left eye, with congestion of the conjunctival vessels and enlargement of the retinal veins of both eyes. The condition is probably due to a vascular tumor in the left orbit which was of negligible size unless filled with blood by some obstruction to the venous flow of blood from the head.

Such cases are not very rare. One reported by Petrov<sup>5</sup> in a woman aged 25 was thought to be due to dilated orbital veins caused by an endocrine disturbance (fig. 40).

#### METASTATIC TUMOR OF ORBIT

Unilateral exophthalmos may be caused by a metastatic tumor of the orbit. Of several cases which I have seen, the following is a good example:

CASE 22.—Mrs. A. G. K., aged 69, had been treated with roentgen rays for some weeks for a lump in the left breast which had first been noticed ten months before I saw her. The progress of her condition was said to be favorable, but for four weeks the left eye had been watering and protruding. The right eye was normal except for beginning cataract. The left eye was inflamed and protruded and was pushed down and out. The exophthalmometer measured 15 and 24 mm. A firm mass could be felt at the upper and inner angle of the orbit and there was a soft protrusion in the orbit down and out, which may have been orbital fat. The retinal veins were very full and tortuous and there were some linear hemorrhages near the disk. Apparently these were due to pressure on the vein after its exit from the eye. The orbital trouble was thought to be metastatic, and palliative treatment was advised (fig. 41).

#### UNKNOWN ETIOLOGY

I will add one case of uncertain origin, and I wonder that I have not seen more such cases:

CASE 23.—M. O., a youth aged 17, in the spring of 1936 fell and bruised the left temporal region slightly. Three or four months later the left eye began to protrude and soon reached its present state and has not changed. Vision is normal, ocular movements are normal and the retinal veins are enlarged and tortuous. The exophthalmometer measures 13 mm. and 20 mm. Physical and roentgen examinations of the nose and sinuses are negative. Nothing abnormal can be felt in the orbit. The external rectus muscle was divided and the interior of the muscle cone was exposed and explored. Nothing abnormal was found. The patient has been examined by many physicians, but a positive diagnosis has not been made (fig. 42).<sup>6</sup>

#### COMMENT

With regard to operative treatment there are two things that I should like to say. One is that, as shown many years ago by Dr. Herman Knapp and advocated by Felix LaGrange, most of these lesions can be reached through the conjunctiva to the outer side of the eyeball,

5. Petrov, A. A.: Case of Unilateral Intermittent Exophthalmos, *Vestnik oftal.* 14: 76, 1939.

6. This patient has since been operated on through the orbital roof and a dermoid tumor removed.

4. Knapp, Arnold: Xanthomatosis of the Orbit, *Arch. Ophth.* 11: 141 (Jan.) 1934.

with the addition of a canthotomy and possibly a temporary resection of the external rectus, and a Krönlein operation is not often necessary. If a Krönlein operation is to be done it is far better to introduce a Gigli saw through the sphenomaxillary fissure and cut with it, as suggested by Magitot, than to do the bone work with a chisel or forceps. One caution in using a Gigli saw is to keep the hands far apart. If they are close together and the arms of the saw are nearly parallel, the saw will invariably bind and break. Spaeth and Wiener have described similar plans and both seem favorable to the Krönlein operation. Spaeth feels that the greater the exophthalmos the more likely is the Krönlein operation not to be necessary. Benedict and Fred Davis have described approaches through the upper and lower lids and through the conjunctival cul-de-sac below, which give good exposure with a minimal postoperative deformity.

1720 Exchange Building.

## LONG-TERM RESULTS IN THE TREATMENT OF EARLY SYPHILIS

PAUL PADGET, M.D.

BALTIMORE

The final evaluation of any system for the treatment of patients with early syphilis must, in the nature of the disease, depend on long term post-treatment observation of a large group of patients. This principle has long been recognized, especially by those who of necessity have attempted the evaluation of modern treatment methods on the basis of a few patients followed for long periods, and larger series in which the period of observation was shorter.<sup>1</sup> These previous authors have not purposely limited themselves; simply because of the time intervals involved, no large group of patients followed for long periods after modern treatment for early syphilis has heretofore been available. It is now possible partially to supply this deficiency.

### THE MATERIAL

From among the patients with early syphilis who had been admitted to the syphilis division it was possible to find 551 who had been completely reexamined five or more years after the termination of the original treatment (i. e., that given during the first two years of therapy). Two hundred and seventy-three of these patients had been followed for more than ten years to a mean of fourteen years of post-treatment observation; the mean in those followed from five to ten years was 7.6 years and for the group as a whole was 10.8 years.

Supported in part by funds provided by the United States Public Health Service.

From the Syphilis Division of the Medical Clinic, the Johns Hopkins Hospital and University.

Read before the joint meeting of the Section on Practice of Medicine and the Section on Pharmacology and Therapeutics at the Ninety-First Annual Session of the American Medical Association, New York, June 14, 1940.

1. Clark, Taliaferro; Parren, Thomas; Cole, Harold N.; Moore, Joseph Earle; O'Leary, Paul A.; Stokes, John H., and Wile, Udo J.: Cooperative Clinical Studies in the Treatment of Syphilis, *Ven. Dis. Inform.* 13: 135 (April) 1932. Stokes, John H.; Cole, Harold N.; Moore, Joseph Earle; O'Leary, Paul A.; Wile, Udo J.; Clark, Taliaferro; Parren, Thomas, and Usilton, Lida J.: Cooperative Clinical Studies in the Treatment of Syphilis, *ibid.* 13: 207 (June), 253 (July) 1932. Vonderlehr, R. A., and Usilton, Lida J.: The Chance of Acquiring Syphilis and the Frequency of Its Disastrous Outcome, *ibid.* 13: 396 (Nov.) 1938. Martenstein, Hans: Syphilis Treatment, *Quart. Bull. Health Organ., League of Nations* 4: 129 (March) 1935. Snodgrass, W. R., and Peters, R. J.: An Analysis of the Results of Treatment of Early, Latent and Mucocutaneous Tertiary Syphilis, *Medical Research Council, Special Report Series*, No. 224, His Majesty's Stationery Office, 1937. Moore and Kemp.<sup>4</sup>

The age distribution of the patients on admission revealed nothing of significance but by race and sex there were more Negro women at the expense of the men of both races than was typical of the clinic population.

### THE FINAL OUTCOME

In the evaluation of results the final outcome was taken as the status observed at the time of institution of any later treatment for syphilis irrespective of the

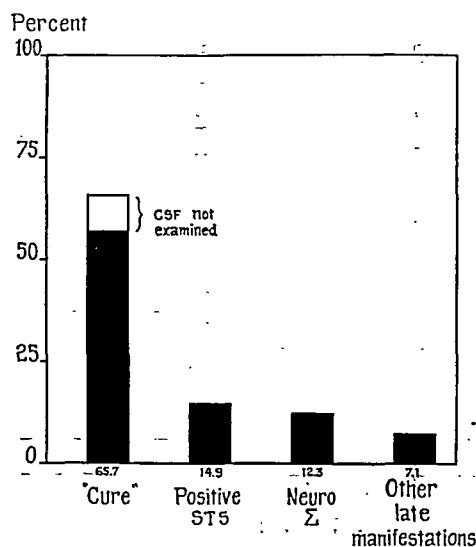


Chart 1.—Final outcome regardless of other factors in 551 patients with early syphilis.

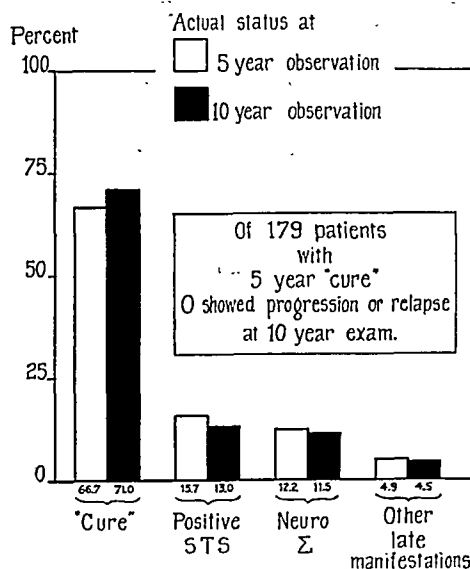


Chart 2.—Comparison of results of examination of 268 patients at approximately five and ten or more years after the termination of treatment for early syphilis. Illustrating the apparent permanence of a five year "cure."

total period of observation. This was necessary to avoid the confusion of attempting to analyze the effect of treatment for late syphilis sometimes scattered over years of sporadic visits. It has the disadvantages of presenting in the overall results of treatment the final worst obtained in life and of excluding from consideration deaths as such. There were seventeen of the latter, ten of which were due to syphilis and seven to a variety of other causes.

The final outcome by this definition is given for the entire group in 551 patients in chart 1.

For the purposes of this study "cure" originally was defined as established by reinfection<sup>2</sup> or by freedom from symptoms and signs of syphilis to careful examination, repeatedly negative results to blood serologic tests, normal roentgenograms of the cardiovascular stripe where taken, and a normal cerebrospinal fluid. Three hundred and fourteen patients (57.0 per cent) satisfied these criteria. In addition there were 48 patients (8.7 per cent) who satisfied all of the criteria save examination of the cerebrospinal fluid. At first dealt with separately, they were found to be distributed so evenly among the larger group that the two were combined, making a total of 362 (65.7 per cent) classified as "cure."

Among the unfavorable results, 82 patients (14.9 per cent) were classified as "positive STS," meaning that

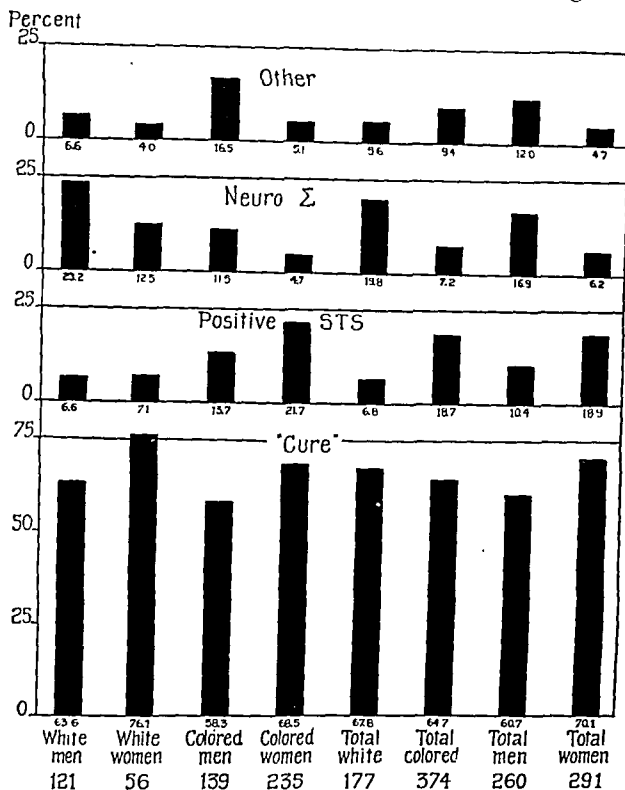


Chart 3.—Final outcome by race and sex. Note particularly among the unfavorable results the incidence of neurosyphilis in white men and of positive STS in colored women. (Vertical columns total 100 per cent.)

complete examination including a test of the cerebrospinal fluid had revealed no evidence of syphilitic infection save that the blood gave a positive reaction to a serologic test.

The more certainly unfavorable results were made up of 68 patients (12.3 per cent) with some form of neurosyphilis and 39 patients (7.1 per cent) with some other late manifestation of the disease. Among these was the dramatic instance of treatment resistance reported by Hood.<sup>3</sup>

#### THE PERMANENCE OF THE FIVE YEAR RESULT

In the following analysis of the results of treatment, no distinction is drawn between the 278 patients who were followed for from five to ten years and the 273 patients who were observed for ten years or more.

2. Halley, C. R. L., and Wasserman, Harry: Second Infection in Syphilis; Its Relation to the Time of Treatment of the First Infection, *Arch. Int. Med.* 41: 843 (June) 1928.

3. Hood, Bowman J.: An Unusual Case of Arspenamine Resistance, *Am. J. Syph., Gonorr. & Ven. Dis.* 21: 97 (Jan.) 1937.

This consolidation is justified by the data of chart 2, in which it is to be noted, in contrast to elsewhere, that the comparison is between the actual status observed and not the arbitrarily defined outcome.

Of the 273 patients who were last examined ten or more years after the termination of the original treatment for early syphilis, 268 had been examined at about a five year period of observation, and on this basis 179 were classified as "cure." At the later examinations none of these manifested progression or relapse. On the contrary, eleven additional patients had converted latent or late syphilis to "cure" without further treatment for three, and there was no significant redistribution of the observed outcome among the remainder in spite of further treatment for most.

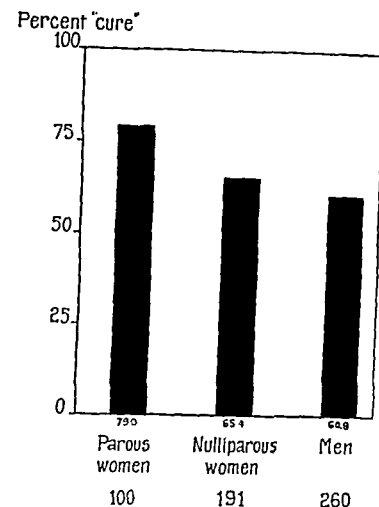


Chart 4.—Apparent influence of sex and pregnancy on final outcome.

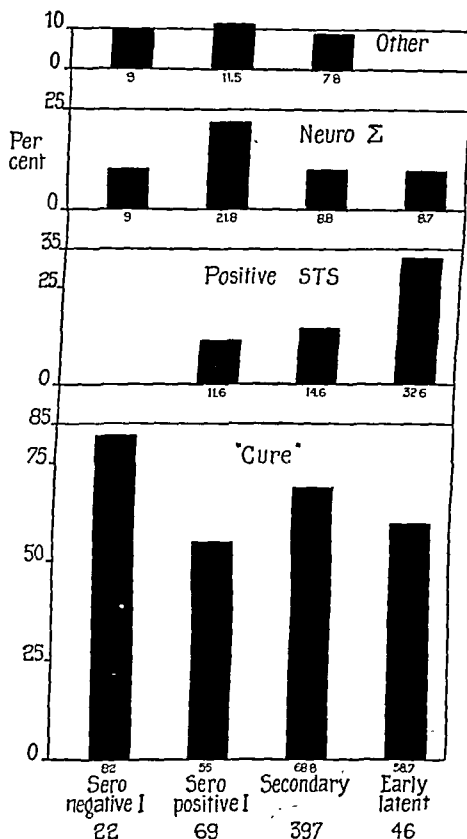


Chart 5.—Influence on the final outcome of the stage of syphilis at the onset of treatment.

This permanence of the five year results among the patients who had done well deserves emphasis, but its greatest importance lies beyond the scope of the present communication.

Analysis of the final outcome by race and sex is illustrated in chart 3. The small group of white women achieved the greatest percentage of "cures" (76.1) and the Negro men the least (58.3) with the other two race-sex divisions between (63.6 and 68.5 for white men and Negro women respectively). Of more importance, however, is that among those who did not achieve "cure" neurosyphilis was two and one-half times as frequent among the white. The Negroes suffered cardiovascular syphilis and other late manifestations more often, but the majority of the unsatisfactory results observed in this race consisted in the persistence of a positive serologic test for syphilis in the blood without other manifestations of the disease. The analysis by sex revealed an equally striking difference; among those

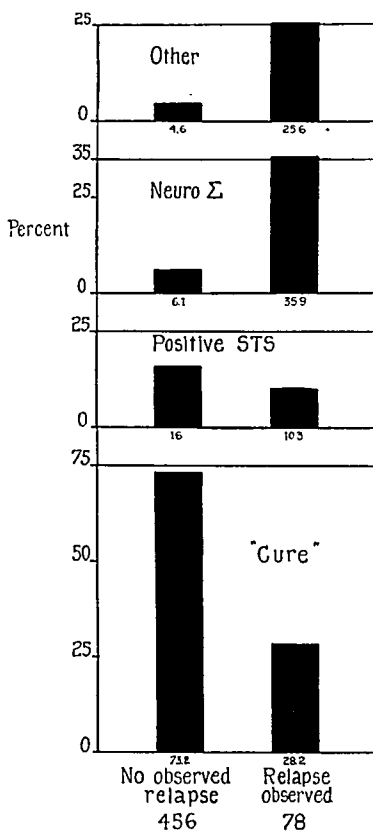


Chart 6.—The ominous prognostic significance of observed relapse.

syphilitic infection. In the present instance, however, it is difficult to be sure that the differences are significant.

The influence on the final outcome of the stage of the disease at the onset of treatment is shown in chart 5. Among the 534 patients who received treatment of any kind, the best results were observed among those who began treatment in the seronegative primary stage, of whom 82 per cent achieved "cure." The worst results obtained to those whose treatment began in the seropositive primary stage, of whom only 55 per cent were so fortunate. In the other groups the incidence of "cure" was 68.8 per cent in those with secondary syphilis at the onset of treatment and 58.7 per cent of those who were in the early latent stage of the disease.

As first pointed out by Moore and Kemp,<sup>4</sup> these differences are probably to be explained by the disrupt-

ing effect of treatment on the immune reaction of the host. This effect is least important in the seronegative primary stage, in which "cure" is so readily effected; it is greatest in the seropositive primary stage, in which

with an unfavorable outcome, neurosyphilis was more than two and one-half times as common among men as among women. Breaking down the sex differences into the further question of the possible influence of pregnancy, chart 4 contrasts the percentage "cures" obtained by the men, the nulliparous women, and those women who had sustained one or more pregnancies concomitant with or subsequent to acquiring syphilis. A much higher percentage of the last group (79) than of either of the former (60.8, 65.6) attained "cure," tending to confirm the previous observations that pregnancy exerts a beneficial effect on

immunity is developing but is imperfect, and is intermediate in the patients with secondary and early latent syphilis, among whom the immune response is reaching or has reached its height. A further development of this thesis offers an explanation for the lower percentage

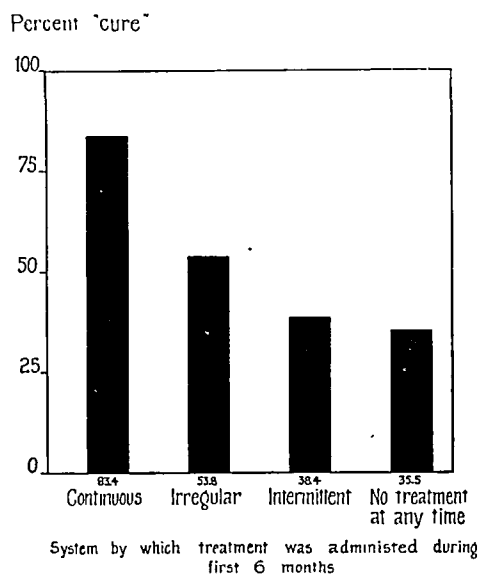


Chart 7.—Outcome with reference to the system of treatment for the first six months.

immunity is developing but is imperfect, and is intermediate in the patients with secondary and early latent syphilis, among whom the immune response is reaching or has reached its height. A further development of this thesis offers an explanation for the lower percentage

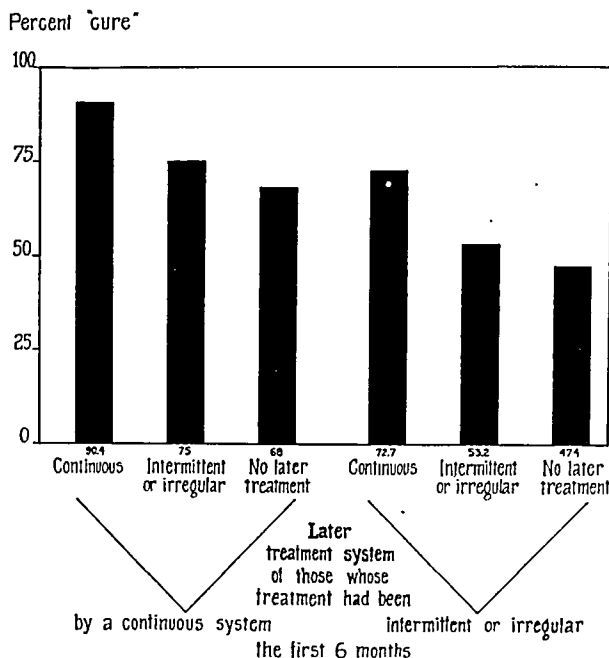


Chart 8.—Outcome with reference to the system of treatment after the first six months. Note that continuation of irregular treatment did not improve the final results.

of "cures" among the patients with early latent syphilis at the onset of treatment, since so many of them (32.6 per cent) were found to be seroresistant at the last examination. It is postulated that in at least some of these the persistence of a positive serologic test in the

4. Moore, Joseph Earle, and Kemp, Jarold E.: The Treatment of Early Syphilis: II. Clinical Results in 402 Patients, *Bull. Johns Hopkins Hosp.* 39: 16 (July) 1926.



blood with no other manifestation of syphilitic infection may reflect the persistence of immunity rather than of disease.

Detailed analysis of the type of unsatisfactory result experienced by the various groups brings out only one other point of significance; neurosyphilis was two and

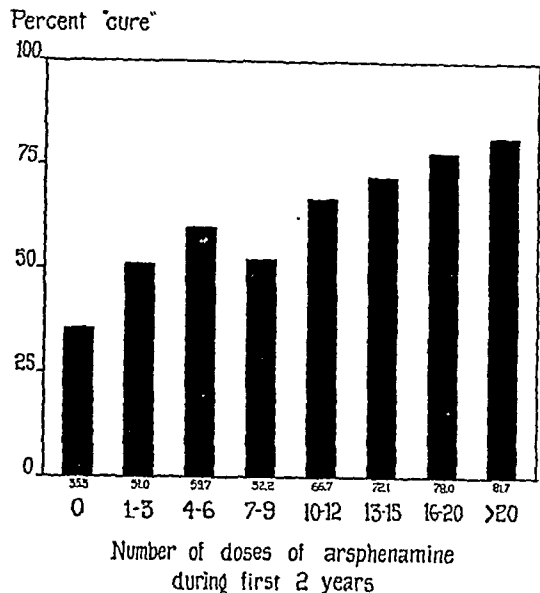


Chart 9.—The relationship between the final outcome and the number of doses of arsphenamine administered during the first two years.

one-half times as common among those who began treatment in the seropositive primary stage as among the others and accounted for the increased incidence of unsatisfactory results in this group.

The ominous prognostic significance of early or intermediate relapse sufficiently dramatic to cause a delinquent patient to return to the clinic is shown in chart 6. "Cure" was nearly three times as common among those who were not observed to relapse as among those who were, and neurosyphilis was approximately six times as common among the latter.

#### RESULTS OF TREATMENT

In the evaluation of treatment the attempt was made to determine the effect of the system by which the treatment was administered, the total amount of treatment in terms of number of doses of arsphenamine, and the effect of the time span over which a given amount of treatment was spread. With a few exceptions the attempted scheme of treatment was by the weekly injection of an arsphenamine in courses, alternating with courses of weekly injections of an insoluble bismuth compound or daily inunctions with mercury according to the system formulated by Moore and Keidel.<sup>5</sup> Almost all the patients were treated with arsphenamine in a weekly dose of 0.3 Gm. for the women and 0.4 Gm. for the men, and all had treatment with heavy metal in amounts approximately equivalent to the arsenical except those who lapsed very early. No attempt was made therefore to compare drugs.

It is here perhaps appropriate to emphasize that, although this system for the treatment of early syphilis has been employed for more than twenty years, it is only now possible to gain an appropriate long term estimate of the results to be obtained from its use. The

several schemes recently proposed for the treatment of early syphilis which involve radical departure from this method do nothing to alter the basic biologic nature of the disease; long term follow-up after treatment has been suspended is necessary to a final revaluation of results.

The final outcome according to the system by which treatment (irrespective of amount) was administered during the first six months is shown in chart 7, and chart 8 gives the final outcome according to the system by which later treatment was carried out.

The superiority of the continuous treatment system over the intermittent and irregular systems is readily apparent. "Cure" was attained by 83.4 per cent of the patients whose treatment during the first six months was by a continuous system, and this increased to 90.4 per cent if treatment after the first six months was likewise continuous. In contrast to this is the fact that only 53.8 per cent of the patients whose treatment was intermittent or irregular during the first six months enjoyed a similar fate, and this outcome was not altered (53.2 per cent) by the further administration of irregular treatment.

On the other hand, even though treatment had been intermittent or irregular during the first six months, later continuous treatment resulted in 72.7 per cent of "cures," while the incidence of "cure" fell to 75 per cent among those whose first treatment was continuous but who later became irregular.

It is doubtless of significance that these figures are approximated by the 68 per cent of "cures" found among those who had had no further treatment after some continuous treatment during the first six months.

Chart 9 presents the outcome with reference to the total number of doses of arsphenamine received during the total period of treatment for early syphilis and the incidence of "cure" rises from 35.3 per cent among the 17 patients who had no treatment at any time to two thirds of those who received from ten to twelve and finally to 81.7 per cent of those who were given more than twenty injections of arsphenamine.

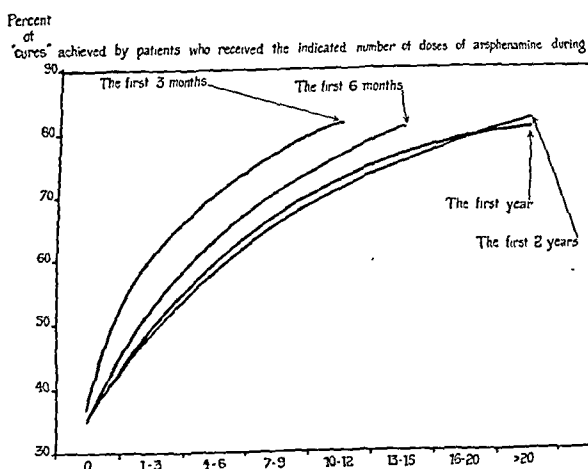


Chart 10.—Illustrating the time factor in syphilotherapy. Patients who received any given amount of arsphenamine did better the shorter the period during which it was given (within the limits of the study).

The incidence of "cure" with regard both to the amount of treatment and to more detailed analysis of the time during which it was given is shown in chart 10. There it may be seen that the final outcome depended not only in a directly quantitative fashion on the number of doses of arsphenamine received but also inversely on

5. Moore, Joseph Earle, and Keidel, Albert: The Treatment of Early Syphilis: I. A Plan of Treatment for Routine Use, Bull. Johns Hopkins Hosp. 39:1 (July) 1926.

the time span during which they were given. Patients who received any stated amount of arsphenamine did better the shorter the time period in which it was administered, serving further to emphasize the necessity of absolute continuity of treatment.

#### SUMMARY AND CONCLUSIONS

1. The results of the long-term post-treatment observation of a group of 551 patients with early syphilis were studied, just less than two thirds of whom attained "cure" as defined.

2. Among those with an unfavorable outcome, there were the same race and sex predilections and relation between outcome and stage of disease at the onset of treatment which previously have been noted by others.

3. Comparative examination at approximately five and ten or more years of observation revealed that all patients who satisfied the criteria of "cure" at the former continued to do so at the latter.

4. The final outcome was found to depend on both type and amount of treatment.

5. The results clearly indicate the superiority of the alternating continuous treatment system and emphasize that continuity should be absolute.

6. The results from irregular treatment were so inferior as strongly to suggest its complete uselessness, especially after the first few injections.

101 West Read Street.

#### ABSTRACT OF DISCUSSION

DR. JOSEPH EARLE MOORE, Baltimore: This is the first large scale long term evaluation of treatment results in early syphilis available. From it may be singled out three points for special comment: 1. Padgett's data justify the opinion that in early syphilis five year "cure" represents permanent "cure." Patients who were clinically and serologically normal five years after treatment ended were still normal after five or more further years of observation. From the purely scientific point of view, the data are as yet inadequate to permit this statement to be too dogmatically made; and the necessity of further long continued observation of these and similar patients still continues, in order particularly to rule out the later development of cardiovascular syphilis, the average incubation period of which is twenty to twenty-five years after infection. From the more purely practical individual and public health point of view, however, the apparent fact of the permanence of five year "cure" is of great importance, since it does permit some relaxation of post-treatment follow-up, after the fifth year of observation, in general medical and clinic practice. 2. The curability of early syphilis is favorably influenced by the amount of arsenical treatment given in the early months, preferably the first three months. The more trivalent arsenical given in this time period the better the chance of ultimate "cure." This fact has perhaps an important bearing on the new "five day treatment" of early syphilis by massive dose and continuous intravenous drip. Nevertheless it is to be observed from Padgett's data that patients who receive so little treatment as only four to six injections of an arsphenamine by conventional divided dose technic have a 60 per cent chance of five year "cure" with practically no risk of hemorrhagic encephalitis or death. The incidence of the serious reaction of hemorrhagic encephalitis with conventional methods of treatment is probably somewhere between one in 15,000 and one in 25,000 patients treated. With the new "five day treatment," the chance of "cure" probably lies somewhere between 70 and 85 per cent, depending on whether mapharsen or neoarsphenamine is used; i. e., a chance of "cure" only 10 to 25 per cent greater than from only four to six conventional doses of an arsphenamine, and no greater than with the best available continuous outline of treatment applied for twelve to fifteen months; but with a risk of the development of hemorrhagic encephalitis of approximately 1 in 100 patients treated, i. e. a risk one

hundred and fifty to two hundred fold greater than with conventional methods. 3. Even with a few injections of an arsphenamine only, patients may be maintained indefinitely in a state of health, as far as syphilis is concerned, in the proportion of about 80 per cent. With the best available conventional methods of treatment, 90 per cent of patients achieve long term "cure" by both clinical and serologic standards, and the amazingly high total of 95 per cent are clinically "cured."

## STREPTOCOCCUS CONVALESCENT SERUMS (SCARLATINAL)

### THE POTENTIALITIES OF TYPE-SPECIFIC POOLS

ERLING S. PLATOÛ, M.D.

PAUL F. DWAN, M.D.

AND

ROBERT E. HOYT, Ph.D.

MINNEAPOLIS

Of the various streptococcus antisera which have been employed to date, scarlet fever antitoxin and pooled convalescent scarlet fever serum have found the greatest favor clinically. Since the rise in popularity of these sera, precise classification of the streptococci has been achieved by serologic methods. Hemolytic streptococci of human origin have been classified by Griffith into thirty known types, of which twenty-six are included in Lancefield's group A while four fall into groups C and G. It has been shown by Green,<sup>1</sup> Bailey,<sup>2</sup> White,<sup>3</sup> Keogh,<sup>4</sup> Allison<sup>5</sup> and de Waal<sup>6</sup> that certain serologic types usually predominate in an epidemic of scarlet fever. Many of the types associated with clinical scarlet fever are proficient in producing erythrogenic toxin and as a result commercial scarlatina antitoxin, which has a high neutralizing titer, has become more and more popular in the treatment of this disease. Some immunologists feel that too much stress has been laid on erythrogenic toxin as a weapon of the hemolytic streptococcus and that not enough consideration has been given to such products as streptolysin, leukocidin, fibrinolysin and the spreading factor of Duran-Reynals and to the organism's invasive ability. Okell,<sup>7</sup> Zinsser,<sup>8</sup> Topley and Wilson,<sup>9</sup> Griffith,<sup>10</sup>

From the Departments of Pediatrics and Bacteriology, University of Minnesota Medical School.

Dr. Joyner of the Lederle research laboratory furnished us with known type cultures and typing sera.

All convalescent serum was obtained from the University of Minnesota serum laboratory. Standard toxin and antitoxin was procured from the National Institute of Health.

Read in the panel discussion on Some Contagious Diseases before the Section on Pediatrics at the Ninety-First Annual Session of the American Medical Association, June 13, 1940.

1. Green, C. A.: The Serological Types of Hemolytic Streptococcus in Endemic Scarlet Fever, *J. Hyg.* **37**: 318-331 (April) 1937.

2. Bailey, J. H.: The Types of Hemolytic Streptococcus Concerned with Scarlet Fever, *J. Bact.* **31**: 80-81 (Jan.) 1936.

3. White, Colin; Rudd, G. V., and Ward, H. K.: The Serological Types of Hemolytic Streptococci Causing Scarlet Fever in Sidney, M. J. Australia **1**: 95-100 (Jan. 21) 1939.

4. Keogh, E. K.: Observations on the Epidemiology of Streptococcus Infections, M. J. Australia **1**: 100-103 (Jan. 21) 1939.

5. Allison, V. D.: Streptococcal Infections, *Lancet* **1**: 1067-1070 (May 7) 1938.

6. de Waal, H. L.: The Serological Types of Hemolytic Streptococcus in Relation to the Epidemiology of Scarlet Fever and Its Complications, *J. Hyg.* **40**: 172 (March) 1940.

7. Parish, H. J., and Okell, C. C.: Two Studies of Streptococcal Infections: Hemolytic Streptococcal Infections in Rabbit; Relationship of Scarlet Fever to Other Streptococcal Infections, *Lancet* **1**: 746 (April 14) 1928. Okell, C. C.: Role of Hemolytic Streptococci in Infective Disease (Milroy Lecture), *ibid.* **1**: 761 (April 9), 815 (April 16), 867 (April 23) 1932.

8. Zinsser, Hans; Enders, J. F., and Fothergill, L. D.: *Immunity: Principles and Application in Medicine and Public Health*, New York, Macmillan Company, 1939, p. 582.

9. Topley, W. W. C., and Wilson, G. S.: *Principles of Bacteriology and Immunity*, Baltimore, William Wood & Co., 1936, p. 1158.

10. Griffith, F.: Types of Hemolytic Streptococci in Relation to Scarlet Fever, *J. Hyg.* **25**: 385 (Nov.) 1926, **26**: 363 (Oct.) 1927; Serological Classification of Streptococcus Pyogenes, *ibid.* **34**: 542 (Dec.) 1934.

Lancefield<sup>11</sup> and others believe that any streptococcus of group A may produce scarlet fever, septic sore throat, erysipelas, paronychia or puerperal sepsis and that "the clinical picture is determined by a number of factors, such as the portal of entry, the tissue infected and, most important of all, by the properties of the

factors as erythrogenic toxin and leukocidin, which are group specific and not type specific, is not affected by the pooling.

A proposed improvement of pooled convalescent serum is type-specific serum in which only good antibody donors are included as determined by test. Hyperimmunization of convalescent donors with a vaccine of the homologous organism and pooling of serums according to type is another possible method of procuring better convalescent serum. Streptococcal infections such as scarlet fever, puerperal sepsis and septic sore throat could by this means be treated with a serum rich in type-specific antibodies as well as in group-specific antibodies.

Studies were first carried out to determine the effect of pooled convalescent scarlatina serum on virulent group A streptococci recovered from scarlet fever cases, and of individual convalescent serum against the homologous organism isolated during the disease. In addition, hyperimmunization of convalescents has been attempted in order to determine whether it is possible to increase the antitoxic and antibacterial titers of donors' serums.

To demonstrate the action of pooled convalescent serum on streptococci, young virulent cultures were added to samples of whole blood. Convalescent serum was then added to one sample. Normal serum was substituted for convalescent serum as a control, and an equal volume of commercial antitoxin diluted one to ten was added to a third sample of blood. The blood used in these studies as a source of phagocytic cells was obtained from infants 1 to 3 months of age and from Dick-positive adults. Coagulation of the blood was prevented by the addition of heparin, and in some cases the blood was defibrinated. To make the amounts of convalescent serum and antitoxin approximate those usually administered clinically, we have in most cases diluted the concentrated antitoxin ten times.

A sample of blood from one source was divided into three portions of 6 cc. each. To the first of these (the control) was added 2 cc. of serum from an infant or a Dick-positive individual, to the second 2 cc. of pooled convalescent serum was added and to the third 2 cc. of commercial antitoxin. The bacterial inoculum was prepared by diluting a twelve hour culture grown on veal-infusion broth until 1 cc. contained from 100 to 300 chains. Two cc. of this dilution was added to each

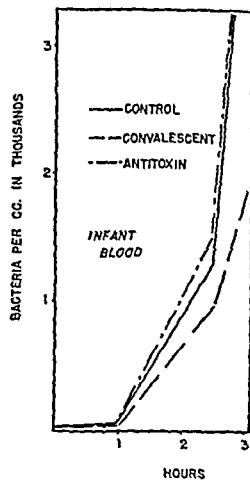


Chart 1.—Comparative bacteriostatic effect.

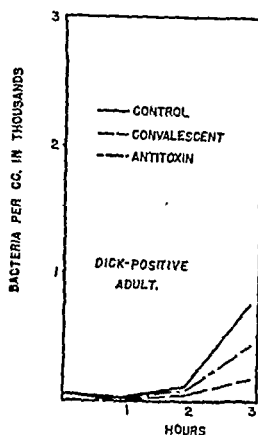


Chart 2.—Comparative bacteriostatic effect.

organism which characterize it as virulent and invasive, together with the toxic substances secreted and the immunologic reactions of the host to these several biological circumstances."

It would seem that the ideal antiserum for treatment of a group A streptococcus infection, whether that infection appears as scarlet fever or some other clinical entity, will be one that is:

1. Rich in antibodies directed against all of the previously mentioned group weapons of the streptococcus.
2. One which contains an abundance of type-specific antibodies.
3. One which is homologous.

Although cellular factors are important in streptococcus immunity, as has been shown by Gay and his co-workers,<sup>12</sup> it is believed as the result of clinical and experimental experience that humoral antibodies, especially opsonins, have a prominent role in the recovery mechanism. Lyons,<sup>13</sup> as a basis for his method of selective immunotransfusion, showed that young virulent streptococci resisted phagocytosis in nonimmune blood and that their phagocytosis could be brought about only by the addition of type-specific opsonins to the blood. These type-specific substances may be procured by pooling convalescent serum from different sources; but such a method necessitates the dilution of each type by the others and thus renders the serum less effective from the standpoint of type specificity. To avoid dilution as much as possible, serum depots now collect convalescent serum early in an outbreak for use during the course of the epidemic. The action of pooled convalescent serum on such toxic

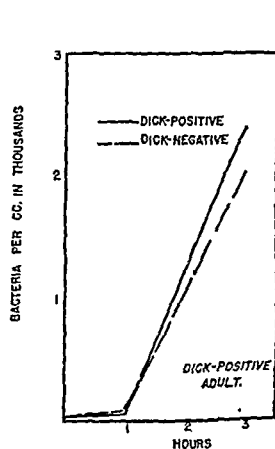


Chart 3.—Comparative bacteriostatic effect.

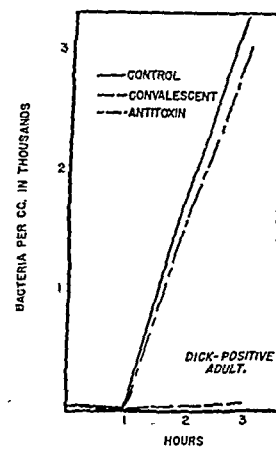


Chart 4.—Comparative bacteriostatic effect.

11. Lancefield, R. C.: Antigenic Complex of *Streptococcus Haemolyticus*: Demonstration of Type-Specific Substance in Extracts of *Streptococcus Haemolyticus*, J. Exper. Med. 47:91 (Jan.) 1928; Chemical and Immunological Properties of Protein Fractions, *ibid.* 47:469 (March) 1928; Chemical and Immunological Properties of Species-Specific Substance, *ibid.* 47:481 (March) 1928; Anaphylaxis with Two Non-Type-Specific Fractions, *ibid.* 47:843 (June) 1928; Anaphylaxis with Type-Specific Substance, *ibid.* 47:857 (June) 1928.

12. Gay, F. P., in Jordan, E. O., and Falk, I. S.: Newer Knowledge of Bacteriology and Immunology, Chicago, University of Chicago Press, 1928.

13. Lyons, Champ: Immunotransfusion and Antitoxin Therapy in Hemolytic Streptococcus Infections, J. A. M. A. 105:1972 (Dec. 14) 1935.

portion of blood and serum, bringing the total volume of each to 10 cc. This made a final dilution of 1:5 for the normal serum and the convalescent serum and 1:50 for the commercial antitoxin. After thorough mixing the various samples were placed in test tubes, stoppered and rotated on a revolving wheel in the 37 C. incubator. The red cells of the blood were tested for compatibility with the convalescent serum added. At varying intervals samples were removed from each mixture,

the number of viable organisms was determined by the pour plate method and smears were stained for determination of phagocytic indexes. After two hours it was usually necessary to make serial dilutions of the blood to obtain a distribution of organisms which would permit accurate counting. The number of organisms per cubic centimeter present at a given time was obtained by deriving the mean count of three plates and multiplying this value by the dilution factor.

It is seen in chart 1 (table 1) that streptococci are capable of growing without interruption in infant blood to which normal serum has been added. Substitution of commercial antitoxin to a sample of the blood, instead of normal infant serum, did not affect the rate of growth. When pooled convalescent serum was substituted for normal serum a pronounced bacteriostatic effect resulted. All tubes in this experiment received an inoculum of 14 organisms per cubic centimeter. By the end of one hour the control and the antitoxin tubes each contained approximately sixty organisms per cubic centimeter, while the mixture containing pooled convalescent serum contained only twenty-five organisms per cubic centimeter. This relative difference persisted for several hours.

The inhibitory effect of convalescent serum as shown in the experiment in which infant blood was used as a source of phagocytic cells is considerably less than that which is shown in subsequent charts illustrating the action of adult blood. This difference may be explained by the well known fact that infant blood contains many less polymorphonuclear leukocytes than does the blood of an adult.

Chart 2 shows the results obtained when blood from a Dick-positive adult was used as a source of phagocytic cells. A striking difference between the effect of convalescent serum on the one hand and commercial antitoxin and normal serum on the other hand is apparent. Again it is seen that commercial antitoxin exerts no antibacterial action *in vitro*. The initial decrease observed in the control tube is probably due to the fact that the individual, though possessing no antitoxic immunity (as shown by the positive Dick test) does have some degree of antibacterial immunity.

Charts 3 and 4 also demonstrate the *in vitro* inhibitory action of pooled convalescent serum in contrast to the negative effect of normal serum and commercial antitoxin when each is added to whole adult blood containing active phagocytes.

In the next experiment (chart 5) the blood of a toxin-immunized Dick-negative individual was inoculated with streptococci and compared with blood from a Dick-positive individual which was inoculated in the same way. No difference in bacteriostatic activity of the two blood samples could be demonstrated. This suggests that, whereas successful immunization to the point of a negative Dick test produces a desirable antitoxic immunity, it brings about no antibacterial immunity as determined *in vitro*.

Clinical evidence of this antigenic inadequacy on the part of erythrogenic toxin is afforded by the

occurrence of streptococcic sore throat in a group of nurses at the Minneapolis General Hospital. Of twelve immunized nurses serving in scarlet fever wards, eleven who were known to be Dick negative contracted streptococcic sore throat, while one nurse who had been immunized but who had failed to become Dick negative

TABLE 1.—*Infant Blood*

Hours	Tube	Count	Dilution	No. per Cc.
0	All.....	14	0	14
1	1. Control.....	12	1:5	60
	2. Convalescent serum.....	5	1:5	25
	3. Antitoxin diluted 1:10.....	11	1:5	55
2½	1. Control.....	137	1:10	1,370
	2. Convalescent serum.....	93	1:10	930
	3. Antitoxin diluted 1:10.....	160	1:10	1,600
4	1. Control.....	396	1:100	39,600
	2. Convalescent serum.....	190	1:100	19,000
	3. Antitoxin diluted 1:10.....	360	1:100	36,000
5½	1. Control.....	360	1:1,000	360,000
	2. Convalescent serum.....	275	1:1,000	275,000
	3. Antitoxin diluted 1:10.....	425	1:1,000	425,000
10	1. Control.....	125	1:1,000,000	125,000,000
	2. Convalescent serum.....	111	1:1,000,000	111,000,000
	3. Antitoxin diluted 1:10.....	159	1:1,000,000	159,000,000

contracted an identical sore throat. The latter nurse developed a mild scarlatinal eruption, which was followed by desquamation. The relatively mild course of all who became ill suggested that their antitoxic immunity may have been beneficial.

A case now under observation further bears out the failure of antitoxic immunity to confer antibacterial immunity. A boy aged 10 was immunized to the point of a negative Dick test. Six months later, while attending school where scarlet fever was known to exist, he contracted a typical "scarlet fever" sore throat with no rash and later developed lymphadenitis and acute glomerulonephritis as complications. A type 13 hemolytic

TABLE 2.—*Dick-Positive Adult*

Hours	Tube	Count	Dilution	No. per Cc.
0	All.....	5	1:5	25
½	1. Control.....	3	1:5	15
	2. Convalescent serum.....	0	1:5	0
	3. Antitoxin diluted 1:10.....	2	1:5	10
1	1. Control.....	1	1:5	5
	2. Convalescent serum.....	1	1:5	5
	3. Antitoxin diluted 1:10.....	1	1:5	5
1½	1. Control.....	4	1:5	20
	2. Convalescent serum.....	2	1:5	10
2	1. Control.....	20	1:5	100
	2. Convalescent serum.....	9	1:5	45
	3. Antitoxin diluted 1:10.....	17	1:5	85
3	1. Control.....	150	1:5	750
	2. Convalescent serum.....	31	1:5	155
	3. Antitoxin diluted 1:10.....	82	1:5	410
5	1. Control.....	4,000	1:5	20,000
	2. Convalescent serum.....	650	1:5	3,275
	3. Antitoxin diluted 1:10.....	2,000	1:5	10,000

streptococcus, which according to Topley and Wilson has been observed as a cause of sporadic scarlet fever, was recovered from the boy's throat.

Moreover, puerperal sepsis due to strains of streptococci which often cause scarlet fever have been found to occur just as commonly in Dick-negative as in Dick-positive individuals by Colebrook<sup>14</sup> and others.

14. Burt-White, Harold; Colebrook, Leonard; Morgan, Gertrude; Jervis, Beatrice J. W., and Harre, Gertrude E.: A Study of Cutaneous Sensitiveness to Scarlatinal Toxin in Pregnancy and the Puerperium, Brit. M. J. 1: 240 (Feb. 8) 1930.

Failure of commercial antitoxin to prevent scarlet fever in several exposed individuals, that we have observed is additional proof that antitoxic immunity in scarlet fever, however desirable, is not operative as an antibacterial immunity. Two of our patients who had serum reactions died of bacteremia and streptococcal laryngotracheobronchitis respectively. Hartshorn and

TABLE 3.—Dick-Positive and Dick-Negative Adult

Hours	Tube	Count	Dilution	No. per Cc.
0	All.....	22	None	22
1	1. Whole blood from Dick-positive adult.....	8.5	1:5	43
	2. Whole blood from Dick-negative adult.....	10	1:5	50
3	1. Whole blood from Dick-positive adult.....	24	1:100	2,400
	2. Whole blood from Dick-negative adult.....	20	1:100	2,000
5	1. Whole blood from Dick-positive adult.....	203	1:1000	203,000
	2. Whole blood from Dick-negative adult.....	164	1:1000	164,000
9	1. Whole blood from Dick-positive adult.....	24	1:1,000,000	24,000,000
	2. Whole blood from Dick-negative adult.....	31	1:1,000,000	31,000,000

Chandler<sup>15</sup> have reported four cases of scarlet fever in which the onset of bacteremia coincided with the beginning of serum disease. The spread of infection by this method has in fact been demonstrated by Burn<sup>16</sup> and the aforementioned authors in animals.

The usual doses (20 cc.) of pooled convalescent serum have been found inadequate in protecting against scarlet fever in a few cases in our experience<sup>17</sup> and it may be that even larger doses of antibacterial serum or combined serum and chemotherapy are necessary in order to provide thoroughly adequate antibacterial immunity.

It should be pointed out that in the antibacterial studies which have been described a relatively large quantity of serum was employed as compared to the amount injected in prophylactic procedures, though

TABLE 4.—Control, Convalescent Serum, Antitoxin

Hours	Tube	Count	Dilution	No. per Cc.
0	All.....	22	None	22
1	1. Control.....	8.5	1:5	43
	2. Convalescent serum.....	3	1:5	15
	3. Antitoxin diluted 1:10.....	13	1:5	65
3	1. Control.....	24	1:100	2,400
	2. Convalescent serum.....	85	1:10	850
	3. Antitoxin diluted 1:10.....	207	1:10	2,070
5	1. Control.....	203	1:1000	203,000
	2. Convalescent serum.....	600	1:100	60,000
	3. Antitoxin diluted 1:10.....	2,000	1:100	200,000
9	1. Control.....	24	1:1,000,000	24,000,000
	2. Convalescent serum.....	240	1:100,000	24,000,000
	3. Antitoxin diluted 1:10.....	Too many	1:100,000	

with the amounts used in the tests the difference in bacteriostatic action of the serums tested was quite striking. Moore and Thalhimer<sup>18</sup> have demonstrated

antibacterial properties in some individual convalescent serums against types 1, 3, 10 and 30.

Since the antitoxic titer of convalescent serum is known to range from only 5 to 10 units per cubic centimeter, an attempt was made to increase the antitoxic level of two recovered scarlet fever patients. These individuals were given the ordinary series of erythrogenic toxin injections used in the Dick immunization.

For purposes of comparison, samples of blood were taken before and after toxin immunization. Measurements of antitoxic immunity were carried out according to the method of the Dicks. Serum from the donors and pooled convalescent serum were compared in this way. Individuals known to be Dick positive were used in making standardizations. Each person was given injections of standard toxin-antitoxin mixtures as well as unknown serum plus standard toxin, thus permitting a comparison to be made between standard and unknown on each reactor.

The results of this experiment as summarized in table 6 indicate that the immunization of scarlet fever convalescents with erythrogenic toxin does not increase the antitoxic immunity of such individuals appreciably.

In spite of the relatively low antitoxic titer of convalescent serum, the clinical results reported by Hoyne, Levinson and Thalhimer<sup>19</sup> following therapeutic doses

TABLE 5.—Dick-Positive Blood

Hours	Tube	Count	Dilution	No. per Cc.
0	All.....	32	None	32
1/2	1. Control.....	0	1:3	0
	2. Convalescent serum.....	0	1:3	0
	3. Antitoxin diluted 1:10.....	(1, 0, 0)	1:3	1
1	1. Control.....	1	1:3	3
	2. Convalescent serum.....	(0, 1, 0)	1:3	1
	3. Antitoxin diluted 1:10.....	(2, 2, 1)	1:3	5
3	1. Control.....	38	1:100	3,800
	2. Convalescent serum.....	2	1:10	20
	3. Antitoxin diluted 1:10.....	30	1:100	3,000
5	1. Control.....	21	1:10,000	210,000
	2. Convalescent serum.....	3	1:1,000	3,000
	3. Antitoxin diluted 1:10.....	24	1:10,000	240,000
9	1. Control.....	126	1:1,000,000	126,000,000
	2. Convalescent serum.....	8	1:2,000,000	8,000,000
	3. Antitoxin diluted 1:10.....	154	1:1,000,000	154,000,000

of only 40 cc. compared favorably with those collected by us<sup>17</sup> at about the same time, following the use of commercial antitoxin in doses fifteen times as large when expressed in antitoxin neutralizing units.

These two groups of cases, listed in tables 7 and 8, were observed at about the same time in nearby mid-western cities, although they are not identical samples. The roughly similar reduction of principal complications in the two series as compared to controls suggests the possibility that factors other than antitoxic titer may explain the results obtained with human convalescent serum.

Some reports on the incidence of complications following the use of antitoxin are by no means as favorable as those tabulated.

Although relatively large doses of convalescent serum are required to match the antitoxic titer of commercial antitoxin, it is believed by some that such quantities of human serum are clinically much more effective than an equivalent amount of commercial antitoxin as expressed in antitoxic units. This is offered as further evidence that convalescent serum is antibacterial or at least that its beneficial effect is not limited to its specific

15. Chandler, Caroline A., and Hartshorn, Mildred: Studies on Possible Correlation between Experimental and Clinical Data Concerning Response of Infection to Serum. *Yale J. Biol. & Med.* 5: 555 (July) 1933.

16. Burn, C. G.; Chandler, Caroline A., and Hartshorn, Mildred: Production of Streptococcus Hemolyticus Bacteremia in Nonspecifically Sensitized Animals. *J. Exper. Med.* 60: 1 (July) 1934.

17. Sako, Wallace; Dwan, P. F., and Platou, E. S.: Sulfanilamide and Serum in Treatment and Prophylaxis of Scarlet Fever. *J. A. M. A.* 111: 995 (Sept. 10) 1938.

18. Moore, Elizabeth, and Thalhimer, William: Immunologic Properties of Scarletina Convalescent Serum. *Am. J. Dis. Child.* 58: 1039 (Nov.) 1939.

19. Hoyne, A. L.; Levinson, S. O., and Thalhimer, William: Convalescent Scarlet Fever Serum: Its Prophylactic and Therapeutic Value; Review of 2,875 Cases. *J. A. M. A.* 105: 783 (Sept. 7) 1935.

antitoxic content. Our own experience with massive intravenous doses of convalescent serum in critically ill patients suggests that this is true.

In an attempt to increase the antibacterial activity of convalescent serums, four donors who had recovered from scarlet fever were inoculated with suspensions of killed virulent streptococci. Two were of unknown type and received type 8 vaccine, while two others were types 2 and 4 respectively and were given vaccine of the homologous type.

The vaccine was prepared by suspending the centrifuged organisms from a veal-infusion broth culture so that each cubic centimeter contained approximately 200,000,000 organisms. The streptococci were killed by heating at 56 C. The convalescent donors were given 0.5 cc. of the vaccine subcutaneously and were bled on the second to the seventh day following. Comparison of the antibacterial power of the serum before and after administration of the vaccine was made in the same manner as described in the previous experiments.

It was thought that the antigenic stimulus provided by the bacterial suspension might cause an exfoliation of antibodies into the blood stream resulting in an increase in antibacterial power. Using whole blood from a Dick-positive adult as a source of phagocytes, to which samples of serum to be tested were added (as described), we were unable to demonstrate any increased antibacterial activity on the part of the donor's serum as the result of the single stimulus employed.

TABLE 6.—*Titers Before and After Immunization*

Donor	Titer Before Immunization	Titer After Immunization
Cameron.....	10 units per cc. serum	10 units per cc. serum
Marshall.....	10 units per cc. serum	10 units per cc. serum

#### COMMENT

From the observations of Ward and Lyons,<sup>13</sup> Fothergill and Lium,<sup>20</sup> Moore and Thalhimer<sup>18</sup> and from our own experiments, it appears that some individuals are deficient in their ability to produce a high degree of humoral immunity after streptococcic infection, while others are proficient. Constitutional make-up, bacterial dosage, occurrence of complications, the antigenic composition of the involved streptococcus (as revealed by Mudd<sup>21</sup>) and perhaps other factors are involved in the adequacy of the immunity resulting from infection. This no doubt explains the uniformity in the action of pooled serum as compared to the variability found in individual samples. If a sample of each donor's serum could be tested by opsonic study prior to its acceptance in a pool, and especially if it could be tested against a homologous type of organism, the serum resulting would be even better than the pools now dispensed by serum depots.

To avoid the necessity of obtaining cultures for typing of all donors, our laboratory is now typing serum directly, using purified M substance from known types of streptococci. Either by typing the organism responsible for the disease or by detection of type-specific antibodies in the serum itself, it is possible to pool serums known to be active according to types

and thus provide undiluted type-specific antibodies. A method of treatment obviously superior to immunotransfusion and even better than pooled convalescent serum can thus be made.

An advantage to be gained by the use of any human convalescent serum is found in the ease and safety with which it can be administered. It has been shown<sup>22</sup> that even concentrated antibody (diphtheria antitoxin) is absorbed at a surprisingly slow rate after intramuscular administration. Clinical observations constantly emphasize the importance of early administration of serum. Some workers stress the quantitative factor in therapy but too few have dwelt on the need for a safe, rapid dissemination of antibodies which specifically combat the peculiarly widespread toxemia as well as the invasive processes of the organism. This is best achieved safely by the intravenous administration of human serum.

#### SUMMARY

The clinical and experimental evidence presented suggests the following points:

1. Erythrogenic toxin, produced in varying amounts by any of Griffith's thirty types of hemolytic streptococci, is important in the pathogenesis of scarlet fever and other streptococcic infections and its prompt neutralization is desirable.

2. Other toxic products of the hemolytic streptococcus, such as leukocidin, fibrinolysin, and spreading and invasive factors have received inadequate consideration.

3. The ideal antiserum for treatment of infections due to group A hemolytic streptococci (including scarlet fever) is one which is rich in both group-specific and type-specific antibodies and which is homologous.

4. Though commercial scarlet fever antitoxin has merit as a neutralizing agent against erythrogenic toxin, it lacks any antibacterial or anti-invasive properties.

5. Pooled convalescent scarlet fever serum in large doses confers considerable antitoxic immunity and in addition an effective antibacterial immunity.

6. Heterologous serum (horse) may cause reactions which can predispose to bacterial spread.

7. Attempts to increase the antitoxic titers of human convalescent donors have been unsuccessful.

8. Hyperimmunization of convalescent donors with streptococcus vaccines did not result in increased antibacterial activity under the conditions of our experiment.

9. Pooling human serums according to antibody activity and type and administration of this product intravenously offer an immunologically sound basis for the serum treatment of group A streptococcus infections.

22. Platou, E. S.: Antitoxin in Diphtheria: A Comparative Study of Usual Methods of Administration with Intraperitoneal Method, *Arch. Pediat.* 40: 575 (Sept.) 1923.

**The Original Materials Vary.**—The same soil that without water is a desert may, under irrigation, produce luxuriant vegetation. On the other hand, no matter how much we may water a rock, we shall be unable to produce a single blossom. So with human beings, the original materials vary, and conditions under which those materials develop into character and personality vary also. It requires the combination of the two, both the material and the life experiences which are called heredity and environment, to explain man as a whole.—Fagre, Marion L., and Anderson, John E.: *Child Care and Training*. Minneapolis, University of Minnesota Press, 1940.

20. Fothergill, L. D., and Lium, Rolf: Value of Commercial, Antibacterial Streptococcus Sera in Hemolytic Streptococcus Infections, *New England J. Med.* 211: 99 (July 19) 1934.

21. Mudd, Stuart; Czarnetzky, E. J.; Lackman, David, and Pettit, Horace: Antigenic Structure of Hemolytic Streptococci of Lancefield Group A: Preparation of Labile, Type-Specific Antigen; Its Identification as Griffith Type-Specific Agglutinin and as Substance from Which a Group-Specific and a Type Specific Hapten Are Derivable, *J. Immunol.* 54: 117 (Feb.) 1938.

A CLINICAL AND PATHOLOGIC STUDY  
OF ORAL DISEASE

BASED ON 2,300 CONSECUTIVE CASES

FRANCIS P. MCCARTHY, M.D.

BOSTON

In presenting this group of cases of oral lesions my primary intention is to give a statistical incidence of diseases and lesions that involve the oral cavity to fill in a hiatus in medical literature. In a compilation of the various groups, some comment is indicated to clarify the various conditions involving specific locations in the mouth and to dilate on some of the special

TABLE 1.—Gingival Lesions

	Office	Clinic	Total
Chronic gingivitis .....	36	43	79
Bismuth gingivitis with pigmentation.....	8	56	64
Gingivitis with hyperplasia.....	18	40	58
Chronic Vincent's gingivitis.....	16	30	46
Acute Vincent's gingivitis.....	12	14	26
Pyorrhea alveolaris .....	4	10	14
Hyperplasia of gingivae (edentulous).....	10	12	22
Acute gingivitis .....	5	13	18
Mucous patch .....	7	8	15
	116	226	342

diseases and some of the more recent theories accounting for oral disease.

The oral cavity has always been a "no man's land" as far as any group of physicians or dentists can claim a special knowledge of the multitude of lesions found in this domain. As the mouth reflects in many instances disease processes elsewhere in the body, it can well be considered the "diagnostic mirror" of the body.

No group of medical specialists is better fitted by training to lead the way in stimulating interest in diseases of the mouth than the dermatologist. The dentist, however, should by election become the diagnostician and be recognized as a stomatologist rather than one whose knowledge is confined to the teeth alone.

With this in mind a course in oral medicine or oral diagnosis was instituted in Tufts College Dental School



Fig. 1.—Hypertrophic stomatitis (palate); chronic irritation from denture.

thirteen years ago, primarily to educate the dentist to recognize lesions of the oral mucous membrane and to utilize his knowledge of dentistry in correlating and interpreting oral lesions. Similar courses are now given in dental schools all over the country and are proving valuable adjuncts to the curriculums of these institutions. With a few exceptions, no such courses are given in the medical

schools in this country, and the knowledge of oral diagnosis by the medical profession is necessarily limited.

Read before the Section on Dermatology and Syphilology at the Ninety-First Annual Session of the American Medical Association, New York, June 13, 1940.

Much misinformation based on insufficient scientific and clinical investigation has been given to both the medical and the dental profession, and in an attempt to "clarify" some of these "issues" this statistical and clinical study of a large group of cases is presented.

The two groups studied include, first, private cases that were referred by dentists and physicians, representing diagnostic problems and those sent for treatment, in which the diagnosis of the disease condition was obvious. The second group represents cases selected for teaching purposes, the sources of which

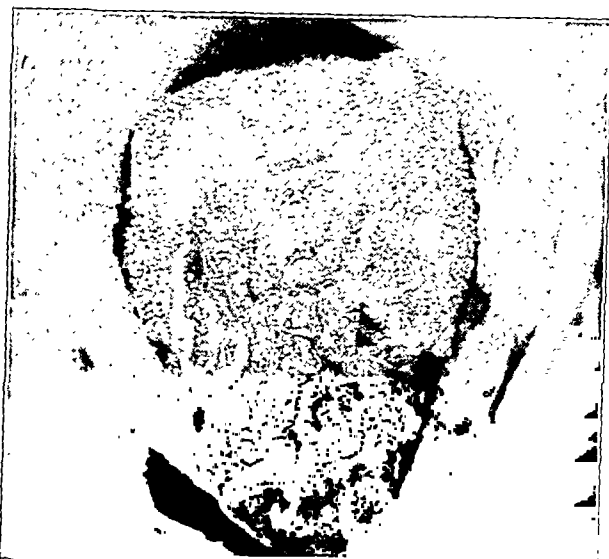


Fig. 2.—Glossitis areata migrans (geographic tongue).

include a large dermatologic outpatient clinic, the dental infirmary and private practice from which cases were referred to the clinic by dentists and physicians. The latter group is not as valuable in determining the incidence of oral disease as the referred and private cases seen in office practice. I have separated the two groups to help determine the incidence and have combined them for a study of etiology, clinical manifestations, pathologic conditions and treatment.

## GINGIVAL LESIONS

Pathologic changes in the gums are almost universal in all decades of life, particularly among the Caucasian race. Certainly as one sees the mouths of persons living under modern conditions one is impressed with the frequency of gingival disease as shown by the mild gingival inflammatory process to the more marked hypertrophic conditions and evidences of infection.

Local evidences of gingival inflammatory changes due to acute or chronic irritation from local causes such as tartar formation or irritation from faulty occlusion and artificial dental appliances account for many of the gingival lesions, but many of these cases reflect some allergic, constitutional condition, blood dyscrasia or drug reaction. There is no group of diseases of the oral cavity that remains so obscure, based on etiology, and it challenges the professions to carry on further studies to solve the many problems involved in gingival lesions.

In compiling this group, I have tried to simplify the terminology without attempting to subdivide the various groups based on etiology. A few cases have been diagnosed as pyorrhea alveolaris, but as the average dentist can readily diagnose this condition it is not referred as



a diagnostic problem, but the etiology of the condition still baffles the medical and dental professions.

The comparatively small number of cases of Vincent's gingival infection is illuminating to most of the medical and dental professions, who are prone to make a diagnosis of this disease on insufficient knowledge. The low grade gingival type of this disease is more common than the local destructive gangrenous lesions seen in other parts of the oral cavity, such as in the tonsillar region.

TABLE 2.—Stomatitis

	Office	Clinic	Total
Chronic aphthous stomatitis.....	40	21	61
Chronic stomatitis .....	22	31	53
Ulcerative stomatitis .....	12	22	34
Acute aphthous stomatitis.....	13	10	23
Traumatic stomatitis .....	3	12	15
Stomatitis (drug lesions).....	5	8	13
Chronic stomatitis (biting habit).....	4	6	10
Gangrenous stomatitis (bismuth poisoning)	0	2	2
	99	112	211

After the World War twenty years ago there was a definite increase in this disease, but in recent years it has definitely become a relatively rare condition based on clinical and bacteriologic examinations.

The chronic form of Vincent's infection is often associated with hyperplastic gingival reaction, and a rich bacterial flora with the presence of Vincent's organisms can be demonstrated under the gingival tabs. This condition is frequently prolonged by overtreatment from repeated medication with irritating and stimulating chemicals.

The classification of gingival lesions, subdivisions such as the allergic group and those related to constitutional disease is avoided, as specific reactions are difficult to demonstrate based on our present knowledge of gingival lesions.

The relatively high percentage of gingivitis with pigmentation due to bismuth in the clinic group is due to a special study of these cases which has been previously reported.<sup>1</sup>

STOMATITIS

In classifying the various types of stomatitis it is necessary to consider the regional distribution of the inflammatory process as well as the mouth as a whole. Again, in a statistical study of this kind one must group certain processes under one heading, as a detailed subdivision is not practicable. The rarity of stomatitis venenata in contrast to the frequency of dermatitis venenata will be noted.<sup>2</sup> This is undoubtedly due to the length of contact of the offending irritant, the natural resistance of the buccal mucosa, the unusually good blood supply, and unknown factors that cause the tissues of



Fig. 3.—Syphilitic atrophic glossitis with leukoplakia.

the mouth to be resistant to external irritants of all kinds.

Galvanism as a cause of local stomatologic lesions has been discussed in the literature for the past decade.<sup>3</sup> In this study I am not ready to accept oral galvanism as a factor in the production of lesions of the oral

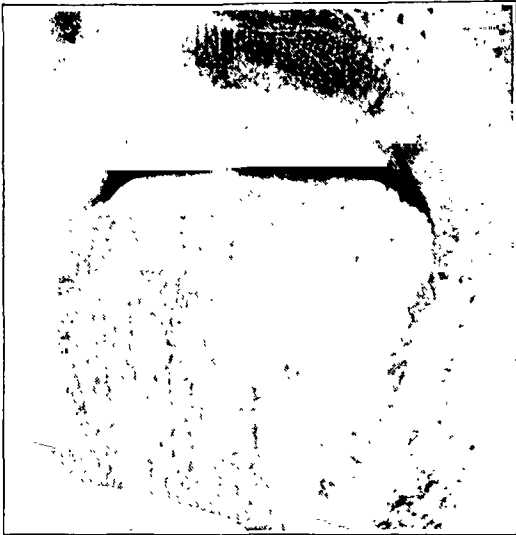


Fig. 4.—Leukoplakia buccalis (grade 4 verrucous carcinoma).

mucosa. It is my belief that lesions which have been attributed to electric currents can be explained by local irritative factors and other causes.

TONGUE LESIONS

Books have been written on diseases of the tongue independent of the oral cavity<sup>4</sup> as a whole, and this classification of tongue lesions is simplified. It will be noted that the diseases lingua nigra and glossitis rhombia mediana are extremely rare conditions as compared with the irritative lesions from local irritative conditions.

I have been especially interested in the development of the tertiary syphilitic lesions of the tongue commonly referred to as the "bald tongue" of syphilis. The mechanism of the production of this particular lesion may be explained by a sequence of pathologic changes, each in turn related to the preceding pathologic tissue reaction. The tongue, a mobile organ subject to mild trauma, receives a heavy dose of spirochetes in the secondary stage, and if the disease is untreated or inadequately treated endarteritis of the smaller vessels results. Later, owing to the interstitial sclerosing process together with the resulting decrease in the blood supply to the highly specialized end organs, the papillae undergo atrophy with the production of smooth, bald areas on the surface of the tongue. These areas are somewhat patchy, and subsequently a leukoplakia develops usually as the result of irritation from the products of combustion and heat in smokers. The leukoplakic lesions may later develop into true malignant growths, which explains the high incidence of carcinoma of the tongue in syphilitic glossitis.

1. McCarthy, F. P., and Dexter, S. O.: Oral Manifestations of Bismuth, New England J. Med. 213: 345-352 (Aug. 22) 1935.

2. Lovenan, A. B.: Stomatitis Venenata: Report of a Case of Sensitivity of the Mucous Membranes and the Skin to Oil of Anise, Arch. Dermat. & Syph. 37: 70-81 (Jan.) 1938.

3. Lain, E. S.: Lesions of the Oral Cavity Caused by Physical and by Physicochemical Factors, Arch. Dermat. & Syph. 41: 295-305 (Feb.) 1940. Reinhard, M. A.; Solomon, H. A., and Goltz, H. L.: Further Experiments in Oral Galvanism, J. Am. Dent. A. 26: 1846-1848 (Nov.) 1939.

4. Spencer, W. G., and Cade, Stanford: Diseases of the Tongue, Philadelphia, P. Blakiston's Son & Co., 1931.



LIP LESIONS

Lip lesions are fairly common, as indicated by the percentage in this group, but there are a large number of patients with herpetic lesions and local inflammatory processes of a transient nature who do not consult medical or dental practitioners. If these were included, the relative percentage of cases involving the lips would

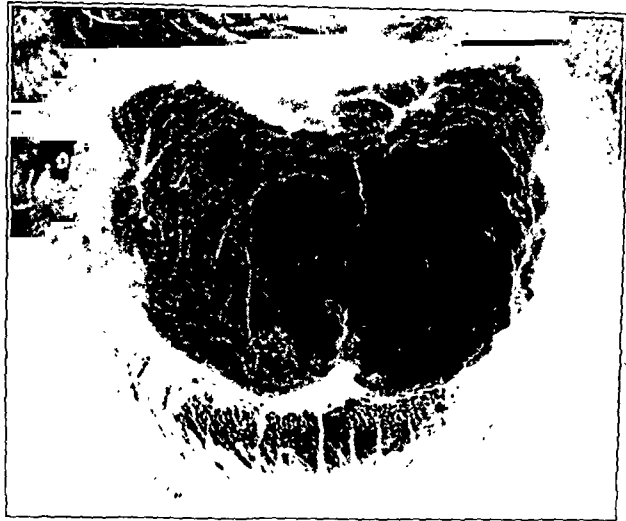


Fig. 5.—Leukoplakia of tongue (grade 4).

be materially increased. Note the small number of cases of cheilitis venenata, indicating that lipsticks of various kinds are chemically inert.

NEOPLASMS AND CYSTS

One will note that the oral cavity is invaded by a large group of neoplasms, both benign and malignant. Except for the rare transitional cell carcinoma at the

TABLE 3.—Tongue Lesions

	Office	Clinic	Total
Glossitis areata migrans (geographic tongue) .....	10	36	55
Congenital fissured tongue .....	14	36	50
Syphilis of tongue:			
Chancre .....	2	2	4
Mucous patch .....	4	6	10
Gumma of tongue.....	4	2	6
Lingua lobulata .....	1	1	2
Atrophic syphilitic glossitis.....	9	36	45
Chronic glossitis .....	20	41	61
Atrophic glossitis (secondary anemia).....	18	14	32
Atrophic glossitis (pernicious anemia)....	5	3	8
Tuberculosis of tongue.....	2	2	4
Ulcerative glossitis .....	11	9	20
Papillitis .....	14	34	48
Glossodynia .....	6	10	16
Lingua nigra (hairy tongue).....	4	5	9
Pseudo-hairy tongue .....	0	2	2
Glossitis rhombia mediana.....	3	2	5
Traumatic glossitis .....	1	5	6
Macroglossia .....	1	0	1
Varicosities .....	2	10	12
	140	236	396

base of the tongue and the rarer adamantine epithelioma, the malignant tumor of the oral cavity is the squamous cell carcinoma. The role of leukoplakia as a forerunner of cancer cannot be determined by this statistical study, but it can be stated that carcinoma frequently arises from the leukoplakic lesion found in syphilitic atrophic glossitis. There are many different types of epulides if one wishes to use the refinements in differentiation of

the cellular structure, but in order to simplify the picture these gingival lesions have been classified into three groups.

The fibromas outnumber any single type of benign tumor, as many tabs of mucosa and fibrosed pedunculated mucous cysts are included in this group.

Mucous retention cysts are rather common oral lesions and are found more frequently on the lower lip and buccal mucosa in relation to the line of occlusion. This can be explained by the importance of trauma as the etiologic factor causing injury to the excretory duct with resulting fibrosis and stricture of the duct.

TABLE 4.—Lip Lesions

	Office	Clinic	Total
Chronic cheilitis .....	13	21	34
Intertrigo labialis .....	7	13	20
Cheilitis exfoliativa .....	9	6	15
Cheilitis glandularis (apostematosa).....	7	6	13
Cheilitis venenata .....	5	3	8
Fissure of lip.....	2	6	8
Chronic lymphangitis .....	3	2	5
Chancre of lip.....	2	3	5
	48	60	108

A high percentage of the submaxillary and sublingual gland cysts (ranula) were associated with calculus either in the main duct or in branches in the parenchyma of the salivary glands.

DERMATOSES

The unusually large percentage of oral lichen planus without cutaneous manifestations is what one would expect in a clinic confined to oral disease. There is considerable difficulty in definitely making this diagnosis in the absence of the characteristic cutaneous lesions, and biopsy specimens are useful in substantiating this diagnosis. Again, oral erythema multiforme without cutaneous lesions may be difficult to differentiate from aphthous stomatitis. The dermatologist again is best fitted to recognize these lesions, although many of the younger dentists have become familiar with these lesions associated with cutaneous diseases.



Fig. 6.—Section of adenoma of palate under low power magnification.

Contrary to the general impression, lupus erythematosus lesions in the oral cavity are not rare. There can frequently be observed small, asymptomatic lesions involving the buccal mucosa of the cheeks in relation

to areas subject to trauma. There may be a close clinical resemblance between oral lupus erythematosus, erosive leukoplakia and the plaque type of lichen planus. A definite differentiation of these conditions can be determined only by a study of biopsy specimens.

The dermatoses characterized by vesicular and bullous lesions in the oral cavity include aphthous stomatitis, herpes buccalis, recurrent erythema multiforme,

TABLE 5.—*Ncplasms and Cysts*

	Office	Clinic	Total	
<b>Squamous cell carcinoma:</b>			118	118
Buccal mucosa .....	10	18		
Lip .....	14	26		
Palate .....	3	2		
Floor of mouth .....	5	4		
Gingivae .....	5	4		
Tongue .....	11	16		
	48	70		
<b>Epulides:</b>			74	74
Fibrous .....	18	24		
Granulomatous .....	12	14		
Giant cell .....	4	2		
	34	40		
<b>Acanthoma</b> .....	8	4	12	12
<b>Fibromas:</b>			73	73
Tongue .....	10	14		
Buccal mucosa .....	8	6		
Lip .....	6	12		
Gingivae .....	2	4		
Palate .....	4	7		
	30	43		
<b>Hemangiomas</b> .....	9	12	21	21
<b>Lymphangiomas</b> .....	2	1	3	3
<b>Granuloma</b> .....	2	4	6	..
<b>Granuloma pyogenicum</b> .....	2	1	3	..
<b>Adamantinoma</b> .....	1	0	1	..
<b>Fibro-anginoma</b> .....	1	0	1	..
<b>Mixed tumors</b> .....	1	0	1	..
<b>Papilloma</b> .....	4	6	10	..
<b>Osteomas</b> .....	0	2	2	..
	22	26	48	48
<b>Cysts</b>				
<b>Ranula</b> .....	21	24	45	45
<b>Mucous cysts:</b>			98	98
Tongue .....	5	8		
Lip .....	28	35		
Buccal mucosa .....	8	14		
	41	57		
<b>Embryonal cyst</b> .....	1	1	2	2
	63	82	145	470

TABLE 6.—*Dermatoses*

	Office	Clinic	Total
Lichen planus (oral).....	12	14	26
Lichen planus (oral and skin) .....	4	10	14
Pemphigus vegetans .....	5	4	9
Oral pemphigus .....	2	0	2
Angioneurotic edema .....	10	4	14
Lupus erythematosus .....	9	15	24
Erythema multiforme .....	10	12	22
Herpes labialis .....	6	14	20
Herpes buccalis recurrent.....	4	3	7
Purpura haemorrhagica .....	2	4	6
Lupus vulgaris .....	0	1	1
Herpes buccalis .....	2	4	6
	66	85	151

oral pemphigus and drug eruptions. Many of these cases present a problem in therapeutics, and investigation of the etiologic factors may furnish the clue in the control of the disease condition.

## BLOOD DYSCRASIAS AND CONSTITUTIONAL DISEASES

The color of the oral mucosa in the anemias is distinctive in cases of severe involvement, and the associated atrophy of the tongue in cases of pernicious anemia and of severe secondary involvement is well known.

Bleeding from the gums with superficial erosive lesions in cases of anemia, granulocytopenia and acute

leukemia may give the first clue to these conditions. The hypertrophic gingival reaction in the more chronic forms of leukemia, particularly the myelogenous type, is particularly diagnostic and again may give the clue to the disease.

Frequently the oral cavity shows changes, especially in the deficiency diseases, so called, with avitaminosis. Pellagra shows rather typical tongue lesions in the



Fig. 7.—Lichen planus dendritic lesions of buccal mucosa.

advanced cases and recently vitamin B<sub>2</sub> (riboflavin) deficiency has been shown to manifest lip and intertriginous lesions at the external commissures.<sup>5</sup> One must not be carried away by literature dealing with the avitaminotic conditions and arrive at hasty conclusions before first ruling out the more common causes of oral lesions.

## DRUG ERUPTIONS IN THE ORAL CAVITY

In the large group of cases in which drug eruptions occurred in the oral cavity only a few were definitely determined to present a relation to ingestion or absorption of drugs. Among the drugs capable of producing lesions in the oral cavity are phenolphthalein, the barbiturates, the iodides and dilantin sodium. The last named drug, used in the treatment of epilepsy, is responsible for a remarkable gingival hyperplastic reaction in up to 50 per cent of patients taking the drug for any considerable period of time. In cases showing a deficiency in vitamin C along with taking the drug, the gingival reactions are earlier and more pronounced.<sup>6</sup>

With the present use of the barbiturates, the various sulfanilamide preparations and dilantin sodium in epilepsy, it is to be expected that oral lesions due to these drugs will definitely increase in number.



Fig. 8.—Lichen planus of tongue, plaque type.

5. Jolliffe, Norman; Fein, H. D., and Rosenblum, L. A.: Riboflavin Deficiency in Man, *New England J. Med.* 221: 921-926 (Dec. 14) 1939.  
6. Frankel, S. I.: Dilantin Sodium in Epilepsy, *J. A. M. A.* 114: 1320-1321 (April 6) 1940.

LEUKOPLAKIA BUCCALIS

In a previous article a group of 316 cases of leukoplakia based on the etiologic factors with a clinical and pathologic gradation were reported.<sup>7</sup> Since that time

TABLE 7.—Manifestations of Blood Dyscrasias and Constitutional Diseases

	Office	Clinic	Total
Atrophic glossitis—secondary anemia.....	18	14	32
Atrophic glossitis—pernicious anemia.....	5	3	8
Acute gingivitis—aplastic anemia.....	2	1	3
Hypertrophic gingivitis—monocytic anemia...	2	1	3
Hypertrophic gingivitis—chronic myelogenous	1	1	2
Acute gingivitis .....	1	1	2
Tonsillitis with ulcerative glossitis (tuberculosis) .....	2	2	4
Tuberculosis cutis orificialis.....	1	0	1
Pellagra .....	1	3	4
Chronic gingivitis (diabetic).....	2	3	5
Chronic atrophic glossitis (avitaminosis).....	2	4	6
	37	33	70

TABLE 8.—Drug Groups

	Office	Clinic	Total
Phenolphthalein			
Bullous stomatitis .....	1	2	3
Barbiturates			
Vesicular eruption .....	2	3	5
Dilantin sodium			
Hyperplastic gingivae .....	1	3	4
Potassium iodide			
Vesicular eruption .....	1	0	1
	5	8	13

many more cases have been added, and investigations on the value of estrogenic substances in the treatment of the conditions are under consideration. The recent



Fig. 9.—Hyperplasia of gums (dilantin sodium therapy for epilepsy).

literature<sup>8</sup> suggesting hormonal deficiencies as an etiologic factor and the application of therapy based on this assumption is not conclusive.

7. McCarthy, F. P.: Etiology, Pathology and Treatment of Leukoplakia Buccalis, Arch. Dermat. & Syph. 34: 612-623 (Oct.) 1936.  
8. Nathanson, I. T., and Weisberger, D. B.: The Treatment of Leukoplakia Buccalis and Related Lesions with Estrogenic Hormone, New England J. Med. 221: 556-560 (Oct. 12) 1939.

Leukoplakia is by far the most common oral mucous membrane lesion, and since the condition is definitely a premalignant hyperkeratotic lesion one cannot over-emphasize the importance of handling these cases.



Fig. 10.—Fordyce's disease (granules of buccal mucosa).

SPECIAL AND MISCELLANEOUS LESIONS

It is not necessary to discuss this particular group, as table 10 indicates the numerical incidence of the various types. The incidence of torus palatinus as shown in this group is undoubtedly lower than the actual incidence, as only the very pronounced cases were recorded. Fordyce's disease, so called, is a common condition and is essentially a normal finding. Only the more noticeable cases are included in this group. Only a small number

TABLE 9.—Leukoplakia Buccalis

Office	Clinic	Total
118	204	322

TABLE 10.—Miscellaneous Lesions

	Office	Clinic	Total
Cancerophobia .....	43	29	72
Fordyce's disease .....	5	41	46
Vincent's infection (tonsil).....	2	2	4
Neuralgia .....	4	8	12
Torus palatinus .....	3	5	8
Exostoses .....	3	4	7
Chanere of tonsil.....	1	0	1
Chanere of buccal mucosa.....	1	0	1
Alveolar abscess .....	7	6	13
Absence of enamel.....	2	0	2
Mottled enamel .....	0	2	2
Xerostomia .....	1	1	2
Parotitis .....	1	4	5
Osteomyelitis .....	1	1	2
Syphilophobia .....	2	0	2
Hemophilia .....	1	0	1
Caleuli (gingival) .....	3	2	5
Alae gingivae .....	1	1	2
Ptyalism .....	5	2	7
Abscess of palate .....	3	0	3
Sinusitis .....	1	4	5
Perleche .....	0	3	3
Perleche .....	0	2	2
Abscess of cheek .....	0	1	1
Argyria .....	1	6	7
Cervical adenitis .....	3	0	3
Cleft palate .....			
	94	124	218

of patients visit a physician or dentist to seek relief of symptoms caused by these lesions.  
These secreting glandular lesions may cause disagreeable symptoms of the lips owing to excessive secretory activity.

## HISTOPATHOLOGY OF ORAL LESIONS

The histopathology of oral lesions is essentially the same as that of lesions which involve the skin. Some variations in the microscopic picture, based on the absence of hair follicles, sudoriferous and sebaceous glands, may be expected, and changes involving the serous and mucous glands present distinctive problems.

Study of the biopsy specimens of the various tumors, infectious granulomas, pigmentary lesions, mycosis fungoides, scleroderma, amyloidosis and some of the

dence to indicate that acute and chronic gingival lesions have an allergic basis.

## CONCLUSIONS

1. Leukoplakia buccalis represents the most frequent and important lesion of the oral cavity.

2. Vincent's infection is on the decrease and now can be classified as an uncommon oral condition.

3. Gingival lesions are the least understood of all oral lesions, and there is opportunity for considerable research to clarify the etiologic factors.

4. Dilantin sodium, a new drug used in the treatment of epilepsy, is a cause of a severe form of hyperplastic gingivitis.

5. Stomatology should be an important subject in both dental and medical curriculums.

371 Commonwealth Avenue.

TABLE 11.—Summary

	Office	Per Cent	Clinic	Per Cent	Total	Per Cent
1. Neoplasms and cysts.....	204	22.0	266	19.3	470	20.4
2. Tongue lesions .....	140	15.1	256	19.0	396	17.2
3. Gingival lesions .....	116	13.0	226	16.4	342	14.8
4. Leukoplakia buccalis .....	118	13.0	204	14.8	322	14.0
5. Miscellaneous and special lesions .....	94	10.1	124	9.0	218	9.5
6. Stomatitis .....	99	11.0	112	8.1	211	9.1
7. Dermatoses .....	66	7.1	85	6.2	151	6.5
8. Lip lesions .....	48	5.1	60	4.3	108	4.6
9. Blood dyscrasias and consti- tutional diseases .....	37	4.0	33	2.4	70	3.0
10. Drug manifestations .....	5	0.5	8	0.6	13	0.6
	927		1,374		2,301	

dermatoses, including lichen planus and lupus erythematosus, can be expected to offer diagnostic information in connection with clinical manifestations.

## COMMENT

Local irritation due to faulty occlusion, artificial dental appliances and dentures is definitely the important factor in the production of focal oral lesions. The physician or dentist must be very thorough in the examination of the oral cavity to rule out these local factors before considering the rarer causes of oral disease.

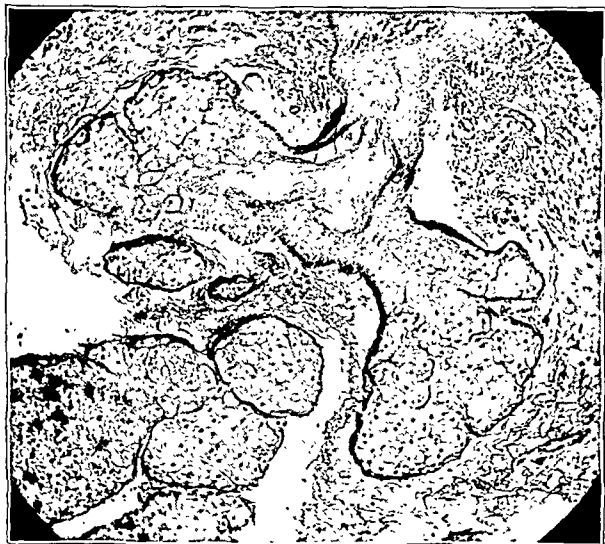


Fig. 11.—Section through Fordyce's granule, showing sebaceous glands.

It is important to recognize the endogenous factors causing oral disease, especially the gingival lesions, the symmetrical vesicular eruptions, the manifestations of systemic disease, the various drug preparations and the dermatoses.

Just how frequently allergic reactions of the buccal mucosa occur is still debatable, but there is some evi-

## ABSTRACT OF DISCUSSION

DR. FRANK J. EICHENLAUB, Washington, D. C.: Dr. McCarthy is to be congratulated for reemphasizing the importance of examination of the mouth. It is impossible to argue with the type of statistics he has presented. Probably many dermatologists are overlooking mouth lesions, and that is why we don't see as many as he has. In the routine admission of patients to the Veterans Hospital in Washington we examined the mouths of 6,468 consecutive patients. Among these were 2,330 cases of dermatoses of various kinds and 233 cases which presented lesions of the mouth, divided as follows: tuberculosis of the tongue, 12; cheilitis glandularis apostematosa, 4; geographic tongue, 21; leukoplakia, 187; monilia of the tongue, 6; torus palatinus, 2, and hairy tongue, 1. In a routine examination of this kind, patients going through from all over the eastern United States and not especially sent in either for skin disease or mouth lesions, most of the mucous membrane lesions were not encountered.

DR. SAMUEL AYRES JR., Los Angeles: I would like to get Dr. McCarthy's opinion regarding the treatment of oral lichen planus, which is one of the most troublesome therapeutic problems in the mouth. I have pretty near gotten to the point of not encouraging patients to undertake treatment for it. In a few instances I have secured more or less complete results with combinations of superficial roentgen therapy, mercuric salicylarsenate and bismuth compounds; but my experience has been quite unsatisfactory. I would be interested to hear whether Dr. McCarthy has anything better to offer.

DR. FRANCIS P. MCCARTHY, Boston: I hoped that there would be more discussion, but I assume that the lack of it is based on the fact that the dermatologist does not examine the mouth as a routine procedure. To obtain clinical material for teaching purposes in a clinic for oral diagnosis, I have become "mouth minded" and plan to examine the oral cavity of about every patient. In the prevention of carcinoma of the mouth I wish to emphasize the value of making patients edentulous as a preventive measure, especially in the male beyond middle life who tends to neglect the teeth and who is a heavy smoker, because it is in this type of case that carcinoma is more prevalent. The edentulous mouth rarely develops a malignant growth even if the individual still continues to be a heavy user of tobacco. With regard to the treatment of oral lichen planus, there is no specific treatment other than the use of mercuric salicylarsenate, the various bismuth preparations, and superficial roentgen therapy. I believe that certain local irritating factors in the mouth, including bridge work and carious teeth, which tend to traumatize the mucous membrane, may be the activating irritants in perpetuating the lesions of lichen planus. I have seen cases of lichen planus with extensive involvement of the oral cavity rapidly disappear in a matter of days or weeks without any form of treatment.

## CARCINOMA OF THE STOMACH

WITH PARTICULAR REFERENCE TO THE SIGNIFICANCE  
OF PERSISTENT SYMPTOMS ASCRIBED TO THE  
STOMACH AND THE MALIGNANT POTENTIALITY OF GASTRIC ULCERS

HOWARD K. GRAY, M.D.

ROCHESTER, MINN.

The seriousness of cancer of the stomach may be emphasized by consideration of the three major causes of death enumerated by Livingston and Pack<sup>1</sup> in a study of end results in the treatment of gastric cancer. These authors have pointed out the fact that our nation has engaged in six major wars since 1776 which extended over a total period of fifteen years. In these fifteen years of war 244,357 American soldiers were killed in action or died of wounds received in action. During the fifteen years of peace, 1923 to 1937 inclusive, 441,912 persons died from injuries received on the highways of the United States. On the basis of 40,000



Fig. 1.—Gastric ulcer: a, Oct. 8, 1937; ulcer 1.5 cm. in diameter on the lesser curvature at the angle of the stomach; b, Nov. 2, 1937; ulcer still present, but with a smaller crater.

deaths a year from cancer of the stomach, as determined from figures furnished to Livingston and Pack by the American Society for the Control of Cancer, the total deaths in the United States from cancer of the stomach for a fifteen year period would be 600,000. Nearly two and a half times as many persons died from cancer of the stomach as were killed in all the major wars in which the United States has been involved.

In the light of present knowledge, only the surgeon can offer a patient afflicted with malignant disease of the stomach the possibility of permanent relief, for early removal of the malignant growth is the only known method of cure. Unfortunately, however, a lamentable disregard of the significance of persistent symptoms referable to the stomach persists among laymen and many members of the medical profession. There is also an equally deplorable tendency to await the development of typical symptoms ascribed in textbooks to

malignant gastric lesions before serious consideration is given to the possibility that a malignant lesion of the stomach exists.

Because of variations in the location and pathogenesis and because of the dissimilarity of the types of malignant lesions of the stomach, the clinical picture of necessity must be inconsistent; often it is vague and ill defined. The late Sir Berkeley Moynihan<sup>2</sup> was impressed by four clinical types of carcinoma of the stomach. In the first and largest group, the symptoms mimicked those of duodenal ulcer but usually the intervals of remission were absent. In the next largest group vague dyspepsia occurred for a varying length of time. Early symptoms of obstruction or hemorrhage as an initial symptom characterized the other two groups. In 24.7 per cent of 287 cases studied by Saltzstein and Sandweiss<sup>3</sup> in which death occurred from malignant disease of the stomach, long-continued indigestion was the prominent feature and in a third of these a typical history of ulcer was obtainable. That half of the patients had been under medical care for ulcer is noteworthy. In

a previous article I<sup>4</sup> mentioned that two distinct clinical groups can be recognized easily. In approximately 75 per cent of the 373 cases of carcinoma of the stomach included in my study there were persistent and unchanged symptoms referable to the stomach and in a fourth of this subgroup the symptoms had been present for more than a year. In 25 per cent of the 373 cases, symptoms referable to the stomach had been present for varying lengths of time but the symptoms had changed recently. The earlier symptoms in this group were similar in most respects to those in the first group mentioned. The symptoms noted recently for the first time consisted in most instances of obstructive features, hemorrhage, rapid loss of weight, anorexia or other features suggestive of a large tumor. These,

unfortunately, are the symptoms that many physicians await before insisting that the patient shall undergo complete investigation with the object of settling the diagnosis.

Latent carcinoma of the stomach, fortunately, is relatively rare; only infrequently will this condition be present. When no symptoms are present, usually nothing can be accomplished, for the disease will be discovered only after death or after the involvement of some distant organ.

One of the reasons why so many physicians await a syndrome characteristic of malignant disease of the stomach before suspecting the presence of a malignant lesion is the impression obtained from some of the widely used textbooks of medicine. In these, "progressive emaciation" has been mentioned as "one of the most constant features," "loss of strength has been found to be proportionate to the loss in weight" and anemia

From the Division of Surgery, the Mayo Clinic.

Read before the Section on Surgery, General and Abdominal, at the Ninety-First Annual Session of the American Medical Association, New York, June 13, 1940.

1. Livingston, E. M., and Pack, G. T.: End Results in the Treatment of Gastric Cancer. An Analytical Study and Statistical Survey of Sixty Years of Surgical Treatment, New York, Paul B. Hoeber, Inc., 1939.

2. Moynihan, Berkeley: Cancer of the Stomach, Practitioner 121: 137-148 (Sept.) 1928.

3. Saltzstein, H. C., and Sandweiss, D. J.: The Problem of Cancer of the Stomach, Arch. Surg. 21: 113-127 (July) 1930.

4. Gray, H. K.: The Clinical and Pathological Factors Influencing the Ultimate Prognosis Following Resection for Carcinoma of the Stomach, Ann. Surg. 97: 882-888 (June) 1933.

is "present in a large proportion of all cases." To illustrate in how large a proportion of the cases a tumor is in evidence when a diagnosis of carcinoma of the stomach was made, one investigator mentioned that in 115 of 150 cases a tumor could be felt. It is obvious that such a description of the "general features" of carcinoma of the stomach is that of advanced carcinoma, and in the vast majority of instances the growth in such cases will have progressed to the point of inoperability.

It is the duty of members of the medical profession to impress on the general public and on their medical colleagues the necessity of seeking medical advice for any digestive disturbance, no matter how vague. If this digestive disturbance does not respond immediately to the usual measures or requires continued treatment for relief, it is the duty of the attending physician to insist on complete investigation in order that the diagnosis may be settled. It should be emphasized again that there is no syndrome characteristic of malignant disease of the stomach. The familiar picture of carcinoma is that of an advanced stage and, if the patient is to receive the greatest benefit from surgical removal of the malignant process, the disease must be recognized before the characteristic signs are present.

#### MALIGNANT POTENTIALITY OF GASTRIC ULCER

A second factor which plays an important role in the maintenance of a discouragingly low rate of operability for carcinoma of the stomach is a widespread lack of appreciation of the malignant potentiality of a gastric ulcer. This does not mean that carcinoma of the stomach develops from gastric ulcer, although in some cases there is ample evidence from clinical and pathologic standpoints to support such a view. Bloodgood<sup>5</sup> has said that "ulcer prevention and ulcer cure are part of cancer prevention and cancer cure." To attempt to debate this problem is outside the scope of this paper.

There is agreement on two points: 1. A chronic gastric ulcer may become malignant. 2. It is impossible clinically and roentgenologically to distinguish positively simple gastric ulcer from early carcinomatous ulcer.

Eusterman and Balfour<sup>6</sup> have stated that "there is as yet no single sign, or any combination of signs, which will determine with absolute certainty whether or not a gastric ulcer is malignant." With this extremely important question to answer accurately, what has been the usual method followed? For approximately three fourths of the patients with gastric ulcer observed for the first time the clinicians at the Mayo Clinic have advised operation. The remaining fourth have been placed on a rigid medical regimen, preferably in a hospital or sanatorium. The disappearance of pain and tenderness, of gross and occult bleeding if once present, and of the niche has been noted by Eusterman and Balfour as the criteria of healing. That such a criterion

will prove accurate in the majority of cases is not doubted. That the niche occasionally may decrease in size or disappear even in the presence of malignant change is not generally known and it is this fact that should be emphasized.

A report of an illustrative case follows:

#### REPORT OF CASE

An unmarried man aged 37 registered for the first time at the Mayo Clinic on Oct. 7, 1937. Eight months prior to his admission, his appendix had been removed elsewhere for backache and epigastric pain which occurred two to three hours after meals. The pain had continued without relief for three months, when he began to have nausea and vomiting. The vomitus contained food he had eaten two or three meals previously. Cholecystectomy was performed elsewhere without relief. The pain was relieved, however, almost immediately after the ingestion of milk.

Roentgenologic examination of the stomach at the clinic on October 8 revealed a gastric ulcer 1.5 cm. in diameter on the lesser curvature at the angle of the stomach (fig. 1*a*). Examination of the gastric contents revealed 64 units of total acid



Fig. 2.—Ulcer on the lesser curvature of the stomach: *a*, June 14, 1938; note penetrating ulcer about 1.5 cm. in diameter at the angle of the stomach with considerable surrounding induration; *b*, March 8, 1939; large ulcer above the angle of the stomach.

and 52 units of free hydrochloric acid. Because the age of the patient and degree of acidity were indicative of a benign lesion, the patient was hospitalized and a rigid medical regimen was instituted. Two weeks later, October 23, the crater of the ulcer had diminished in size and was then about 1 cm. in diameter. Coincident with the improvement as revealed by the roentgenogram, the patient enjoyed remarkable subjective improvement. He was reexamined ten days later (November 2), when it was observed that the ulcer was still present but that the crater was said to be smaller than at the time of the last observation (fig. 1*b*). The patient was dismissed with instructions to return at the end of two months for further examination and to follow a rigid ambulatory regimen about which he had been carefully instructed.

When the patient returned on December 27, he reported that he had been doing well. He had not had gastric pain, but pain about both shoulders had been somewhat disabling. Roentgenologic examination revealed a crater that was about the same size as at the last examination, and in addition there was a duodenal ulcer. The patient was allowed to continue the conservative treatment and he was instructed to return in one month for another examination. However, he did not return until six months later, June 13, 1938. At this time all his old symptoms had recurred and on roentgenologic examination a penetrating ulcer, about 1.5 cm. in diameter with con-

5. Bloodgood, J. C.: Tumors of Stomach, in Lewis, Dean: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1929, vol. 6, chapter 8, pp. 1-107.

6. Eusterman, G. B., and Balfour, D. C.: The Stomach and Duodenum, Philadelphia, W. B. Saunders Company, 1935, pp. 453, 457-462.

siderable surrounding induration (fig. 2a), was visualized on the lesser curvature at the angle of the stomach. Total acids at that time measured 66 units and there were 56 units of free hydrochloric acid in the gastric contents. Because of the recurrence or reactivation of the gastric ulcer in spite of rigid medical management, operation was advised and refused.

Nine months later the patient reappeared for examination. Roentgenologic examination demonstrated a rather large ulcer on the lesser curvature above the angle of the stomach (fig. 2b). There were 60 units of total acid present in the gastric contents and 44 units of free hydrochloric acid.

At operation on March 11, 1939, exposure was made through a primary midline incision in the upper part of the abdomen and a large ulcerating process was revealed on the lesser curvature of the stomach near the angle. Marked induration was associated with this lesion, which extended along the lesser curvature and into the gastrohepatic omentum as far as the insertion of the esophagus. A lymph node near the insertion of the esophagus was removed and sent to the pathologic laboratory for microscopic examination. This was found to be adenocarcinoma grade 3 (on a grading basis of 1 to 4). Because of the extension of the malignant process, the growth was considered inoperable and the wound was closed as an exploration. The patient was sent home eighteen days later and died two months after operation.

#### COMMENT

Did the gastric ulcer that was first visualized nearly two years before the death of this patient undergo a malignant change? Was the ulcerating process malignant from its beginning? Was the malignant process entirely independent of the gastric ulcer and a coincidental lesion? Unequivocal answers to these questions are impossible to obtain. It should be stressed again that the exact nature of an ulcerating lesion of the stomach can be obtained only by means of microscopic examination. This being so, the burden of the responsibility rests on the shoulders of the person who fails to recognize the malignant potentiality of a gastric ulcer in spite of its appearance on roentgenologic and gastroscopic examination, in spite of the age of the patient, the characteristic history of a benign lesion, the presence of appreciable quantities of free hydrochloric acid in the gastric contents, and particularly, as is so vividly illustrated by this case, in spite of improvement in the appearance of the lesion when observed repeatedly by an expert roentgenologist. The case reported herein is representative of an appreciable number of cases in my experience within recent months.

#### SUMMARY AND CONCLUSIONS

The significance of carcinoma of the stomach has been emphasized by Livingston and Pack, who noted that nearly two and a half times as many persons died from cancer of the stomach in fifteen years of peace as were killed outright or died as a result of wounds received during fifteen years in which the United States has been at war. It is important to consider the possibility of carcinoma of the stomach particularly when symptoms referable to the stomach do not subside and disappear after the administration of simple remedies. Furthermore, it should be remembered that there is no syndrome characteristic of malignant disease of the stomach. The widespread impression that a gastric ulcer cannot be malignant if improvement occurs which is verified by observation at intervals by a competent roentgenologist is false.

The malignant potentiality of any ulcerating lesion of the stomach should be recognized.

#### ABSTRACT OF DISCUSSION

DR. ALTON OCHSNER, New Orleans: Physicians have been too much in the habit of thinking of carcinoma as expressed in late manifestations. Dr. Gray has emphasized the importance of the early manifestations. I would emphasize the fact that frequently the symptoms are not referable to the stomach. In our clinic we have seen six patients who had been admitted to the hospital with inoperable carcinoma who in periods of time varying from six to fourteen months previously have had an appendectomy done through a small buttonhole incision. These patients had the same symptoms at the time the appendectomy was done, that is, at the time they were admitted to the hospital; in other words, they had their carcinoma at the time the appendectomy was done. This disease, which occurs as frequently as it does (in 2 per cent of autopsies at the Charity Hospital there was a carcinoma of the stomach), should be operated on earlier. The one case which Dr. Gray mentioned is interesting. Dr. Julius Bauer has studied 200 or 300 of these patients with carcinoma of the stomach. He has followed their family histories and found that patients with carcinoma of the stomach have relations who have either benign peptic ulcers or gastric carcinoma indicating a congenital predisposition to gastric lesions. Dr. Bauer has come to the conclusion that a patient with an ulcer who has a history of ulcers in his family has so great a possibility of developing cancer that a gastric resection should be done even though, as far as one can determine, the lesion is benign. I asked Dr. Gray whether he knew anything about the family history in his case, and he stated that there was no history of cancer in the family but that he did not know whether there was any history of gastric ulcer. We have been rather negligent in getting the family histories concerning a benign lesion, and I think possibly Julius Bauer's suggestion may be of great value.

DR. W. BARCLAY PARSONS, New York: Variations of that tragic case reported by Dr. Gray are far too common in all our larger hospitals. Whether or not cancer develops on ulcer is a point of great academic interest. It is of far greater practical importance, however, that any patient with a gastric ulcer should be suspected of having carcinoma. That is the first point. The second point is that with many smaller gastric lesions the gastroscope in the past few years has proved an instrument of real value. The third point I want to make is that patients with gastric ulcer should be hospitalized and should be observed frequently radiographically. All of us have been at fault in examining a patient, having a roentgenogram made, putting him on an ulcer diet, having another roentgenogram made and then letting the patient go home to come back in two or three months. But the patient doesn't come back or he is back in the hospital or some other hospital with inoperable carcinoma of the stomach. The incidence of those cases is not great, it is not a large number, but they are certainly important and it is a group large enough to subject the patients who have only a simple gastric ulcer to the more rigid regimen. One should insist on complete healing, as far as one can tell by roentgen evidence, and if one can check that with gastroscopic examination one will avoid a large number of cases of unrecognized early carcinoma of the stomach.

DR. HOWARD K. GRAY, Rochester, Minn.: I regret that Dr. Finney could not be here, for no one in our time has contributed more than he to the subject of surgery of the stomach. Dr. Ochsner mentioned the question of symptoms referable to other organs and it reminded me of an extremely important symptom which must be recognized as being possibly associated with a malignant lesion of the stomach. This symptom is secondary anemia. If the cause of any type of anemia cannot be determined, the physician or surgeon should examine the patient carefully for the presence of a malignant lesion of the stomach. I was not familiar with Dr. Bauer's finding of a family history of gastric ulcer in patients suffering from cancer of the stomach. I believe that Dr. Ochsner's suggestion that we inquire more definitely into this question is an excellent one, and that if such a course was followed it would give some valuable information. Dr. Parsons' question has raised in my



mind an important point that I should like to stress, and that is this: Approximately 9 per cent of malignant ulcers of the stomach are diagnosed by competent roentgenologists as being benign. Competent roentgenologists will admit that it is impossible in many instances to make a definite distinction between a malignant ulcer and a benign ulcer. We know that the gastroscopist cannot tell us definitely, and neither can the pathologist tell us, even when he has the opportunity to make a gross examination of the tissue, whether or not a specified lesion is malignant. Therefore one is expecting too much of the clinician to ask him to answer definitely this extremely important question. The question naturally would arise: Why will a malignant ulcer show evidence of apparent improvement in healing under the observation of competent roentgenologists? Schindler has shown that the malignant process may fill in the crater of the ulcer and almost completely obliterate the deformity observed in the roentgenogram. There are also other artefacts that might contribute to a false roentgenologic appearance of healing. Food particles may be caught in the crater or overlapping of the opaque shadow may have taken place or material may be contained in the retrogastric portion of the duodenum behind the ulcerating lesion, all of which might confuse the roentgenologist in his interpretation of that shadow.

## CHROMOBLASTOMYCOSIS

### REPORT OF THE SIXTH CASE FROM CONTINENTAL UNITED STATES

C. W. EMMONS, Ph.D.

WASHINGTON, D. C.

HOWARD HAILEY, M.D.

AND

HUGH HAILEY, M.D.

ATLANTA, GA.

Chromoblastomycosis is a fungous disease which, although rare, is worldwide in distribution. Five cases have been reported in continental United States. One of these, the first case recorded in medical literature, was reported in 1915 by Medlar<sup>1</sup> and Lane<sup>2</sup> from Boston, and the etiologic agent was named *Phialophora verrucosa*. The second case<sup>3</sup> in continental United States (which was from Texas) and the fourth<sup>4</sup> (from St. Louis) were also caused by this fungus. The third case<sup>5</sup> from this continent was reported from North Carolina. That case, the fifth<sup>6</sup> (from Philadelphia) and the sixth, which we are now reporting from Atlanta, Ga., were caused by a related fungus which Brumpt<sup>7</sup> named *Hormodendrum pedrosoi* when he studied the first known South American cases. The latter fungus has been the etiologic agent in most of the studied cases from other parts of the world (including those from Puerto Rico<sup>8</sup>); the relationship between the two pathogens will be discussed in a later paragraph.

Read before the Section on Dermatology and Syphilology at the Ninety-First Annual Session of the American Medical Association, New York, June 14, 1940.

1. Medlar, E. M.: A Cutaneous Infection Caused by a New Fungus, *Phialophora Verrucosa*, with a Study of the Fungus, J. M. Research 32: 507-521, 1915; A New Fungus, *Phialophora Verrucosa*, Pathogenic for Man, Mycologia 7: 200-203, 1915.

2. Lane, C. G.: A Cutaneous Disease Caused by a New Fungus (*Phialophora Verrucosa*), J. Cutan. Dis. 33: 840-846, 1915.

3. Wilson, S. J.; Hulsey, Sim, and Weidman, F. D.: Chromoblastomycosis in Texas, Arch. Dermat. & Syph. 27: 107-122 (Jan.) 1933.

4. Moore, Morris, and Mapother, Paul: Chromomycosis of the Face: Report of a Case and a Study of the Causative Organism, *Phialophora Verrucosa*, Arch. Dermat. & Syph. 41: 42-54 (Jan.) 1940.

5. Martin, D. S.; Baker, R. D., and Conant, N. F.: A Case of Verrucous Dermatitis Caused by *Hormodendrum Pedrosoi* (Chromoblastomycosis) in North Carolina, Am. J. Trop. Med. 16: 593-619 (Sept.) 1936.

6. Weidman, F. D., and Rosenthal, L. H., to be published.

7. Brumpt, Emile: Précis de parasitologie, ed. 3, Paris, Masson & Cie, 1922, p. 1105.

8. Carrión, A. L.: Chromoblastomycosis in Puerto Rico, Puerto Rico J. Pub. Health & Trop. Med. 14: 37-55 (Sept.) 1938. Carrión.<sup>12</sup>

Another case, one in Miami, is also known,<sup>9</sup> but a report of this case has not yet been published. The paucity of reported cases may be an indication of an actual rarity of the disease. Probably, however, many unrecognized and unreported cases occur in the United States.

The scattered distribution of the disease, as shown on the accompanying map (fig. 1), the lack of familial spread and other epidemiologic evidence indicate that the disease, while geographically widespread, is not at all contagious. In many cases there has been a history of injury by wood or vegetation preceding the development of the lesion.

Classic chromoblastomycosis is a chronic and slowly progressing disease characterized clinically by the presence, usually on the leg or foot, of lesions which may be pink or violaceous and verrucous or papillomatous and may become elevated as much as 10 mm. above the surface of the skin. In some of the lesions proliferation of the infected tissue produces pedunculated cauliflower-like excrescences, the uneven surface of which readily ulcerates. A moderate degree of elephantiasis often develops. Typical lesions of this type usually develop only after many years' duration. Four of the five cases previously reported from continental United States differed widely from this type. Weidman and Rosenthal<sup>6</sup> have recently analyzed the cases of chromoblastomycosis which are unusual as to clinical type or anatomic location. The character of the lesions on the foot may be modified by factors such as the pressure of a shoe.

Our case, while not unique, adds another to the list of cases which differ from the classic type. Its unusual clinical features are probably a reflection of the early stage at which the diagnosis was made and therapy begun. We are reporting this case because of the atypical appearance and location of the lesion, the good response to therapy (perhaps also dependent on the short duration of the infection), the apparent rarity of the disease and the stimulation it may give to a search for additional cases in the United States.

### REPORT OF CASE

A white man aged 68, a farmer, came to the Atlanta Cancer Clinic thinking that he had a cancer. The lesion (fig. 2), which was of three months' duration, was on the dorsum of the left wrist. It was 4 cm. in diameter, elevated, a bluish red (livid), boggy to the touch, with multiple points of discharge. The clinical appearance suggested blastomycosis, and that diagnosis was at first made. Cultures were made from the pus. A dark colored fungus which was typical of *Hormodendrum pedrosoi* grew in the cultures, and the diagnosis was accordingly changed to chromoblastomycosis. No biopsy specimen was taken. The clinical features differed so widely from those of a typical chronic case of chromoblastomycosis that the diagnosis was possible only by laboratory methods.

The patient received 150 roentgens on the day he was first seen and 75 roentgens two weeks later. Saturated solution of potassium iodide was administered, beginning with 30 drops after each meal, the patient receiving a total of 90 drops on the first day. Each dose was increased by 1 drop on the following day and on each succeeding day until 50 drops was being taken after each meal (total daily dosage 150 drops) on the twentieth day of treatment. The patient was then instructed to reduce the daily dosage by similar steps until the dosage was back at 30 drops three times a day, at which dosage it was continued. After three months the patient was clinically well and remained so to the time of his accidental death a few

9. Personal communication from Drs. Wiley Sams and Fred D. Weidman.



months later. The period during which the patient remained under observation after his apparent cure was short for a guaranty of cure in this disease, but the lesion appeared to be completely healed.

The fungus isolated from this patient (fig. 3) is entirely typical of *Hormodendrum pedrosoi*. It has the gross and morphologic features of other strains of this fungus isolated in other parts of the world. On an acid dextrose agar medium after four weeks' growth at room temperature the fungus colony is about 4.5 cm. in diameter, with the shape of a low cone about 7 or 8 mm. high. It is a dark olivaceous, but some degree of zonation is apparent, the colors varying from gray-green or blue-green in a narrow zone at the periphery to olive at the center. The surface is covered with short, delicate, ascending aerial hyphae which appear grayish and through which the darker colors of the mycelial mat and substrate hyphae can be seen.

In well developed spore heads there is an arborescent development (figs. 4A and B) resembling that seen in saprophytic species of *Hormodendrum* (*Cladosporium*). Because the branching chains of dark colored spores break apart so readily, this feature is difficult to demonstrate unless slide cultures are very carefully prepared and studied or unless a plate culture is viewed from



Fig. 1.—Geographic distribution in continental United States of reported cases of chromoblastomycosis. Circles, *Phialophora verrucosa*; triangles, *Hormodendrum pedrosoi*.

above with the low powers of the microscope. In a preparation mounted for microscopic study, by teasing out material in a mounting fluid, most of the spores seen will be broken loose from the conidiophores (fig. 4C). In most of the conidiophores no elaborate system of branching spore chains is formed. A more depauperate type of sporulation is substituted in which the spores are borne acropleurogenously—that is, at the tip and along the sides of the conidiophore (fig. 4D). This is the type of sporulation referred to in studies of this fungus as the *Acrotheca* type of sporulation. Various combinations of the two methods of development can be found (figs. 5A and B). An even more reduced type of sporulation is shown in figure 5C. Here clusters of spores are borne on very short lateral conidiophores, or they may even be sessile on the vegetative hyphae. Finally, a few spores are borne (fig. 5D) in the same manner as those of *Phialophora verrucosa*, the other common etiologic agent of chromoblastomycosis. This type of sporulation, only recently demonstrated in *Hormodendrum pedrosoi*,<sup>10</sup> indicates the existence

of a close relationship between the two etiologic agents of the disease.

The appearance of colonies and the microscopic morphology vary to some extent between different strains of this fungus. These variations are described in detail elsewhere and need not be reviewed here.

*Hormodendrum pedrosoi* is similar to related species of molds which are commonly present on dead grass



Fig. 2.—Lesion of chromoblastomycosis on wrist.

and other vegetation. These molds are classified as species of *Hormodendrum* in many mycology laboratories. In this paper we are using the name which was originally given to this pathogenic species by Brumpt,<sup>7</sup> namely, *Hormodendrum pedrosoi*. Thom<sup>11</sup> has recently pointed out that this generic name is a synonym of the older name, *Cladosporium*. We recognize the claim to priority of the generic name *Cladosporium* but are not now prepared to recommend a change in name. There have been numerous other proposed revisions in nomenclature<sup>12</sup> but they will not be reviewed at this time. Any change which could be made at the present time would, we feel, be a temporary one, probably requiring another change in the near future. *Hormodendrum pedrosoi* is obviously related to saprophytic species common on vegetation, but we do not yet know how close this relationship is or whether *Hormodendrum pedrosoi* is a depauperate species of the genus growing normally in this environment or whether it is a mutant arising under the influence of association with animal tissue. There is, moreover, a relationship with the other common etiologic agent of the disease, *Phialophora verrucosa*, which is not yet fully understood.

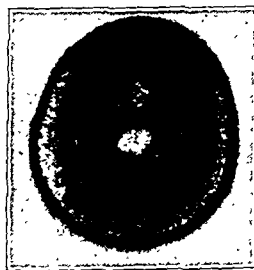


Fig. 3.—Strain of *Hormodendrum pedrosoi* isolated from the subject of the present report. On cornmeal agar after two weeks' incubation at 30°C.

fungus the *Phialophora* type of sporulation occurs, although very rarely in most strains. This report was

11. Thom, Charles: Naming Molds, *J. Washington Acad. Sc.* 30: 49-64, 1940.

10. Emons, C. W., and Carrión, A. L.: The *Phialophora* Type of Sporulation in *Hormodendrum Pedrosoi* and *Hormodendrum Compactum*. *Puerto Rico J. Pub. Health & Trop. Med.* 11: 703-710 (June) 1936.

12. Moore, Morris, and deAlmeida, Floriano Paulo: New Organisms of Chromomycosis, *Ann. Missouri Bot. Garden* 23: 543-552, 1936.

Negroni, Pablo: Estudio micológico del primer caso argentino de cromomycosis *Fonsecaea* (n. g.) *pedrosoi* (Brumpt, 1921), *Rev. d. Inst. Bact.* 7: 419-426 (March) 1936. Carrión, A. L.: *Puerto Rico J. Pub. Health & Trop. Med.*, to be published.

confirmed by Conant<sup>5</sup> and by Moore.<sup>12</sup> Conant<sup>13</sup> made the further important observation that one of the species of *Cadophora*, *C. americana*, is identical with *Phialophora verrucosa*. The species of *Cadophora* are commercially important because they cause an undesirable staining and decay of wood pulp. There is therefore a relationship, as yet imperfectly understood, between the common saprophytic species of *Hormo-*

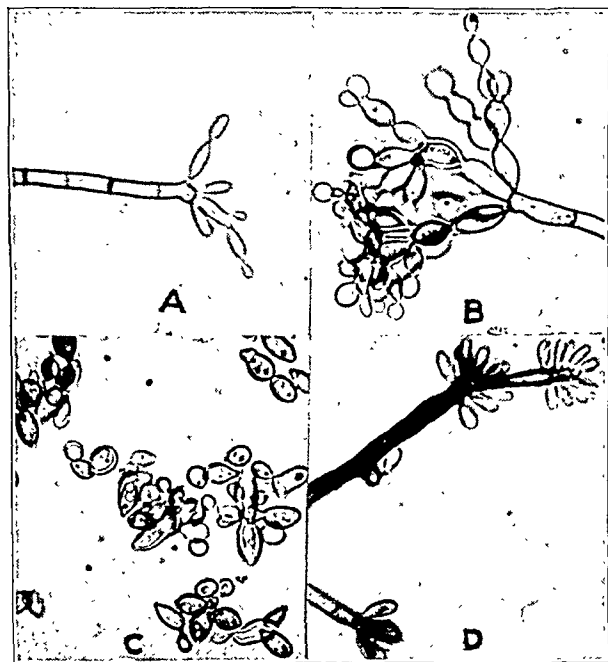


Fig. 4.—A and B, dendroid spore heads from cornmeal agar slide culture; C, spores dissociated from the conidiophore; D, the "Acrotheca type" of sporulation in *Hormodendrum pedrosoi*.

dendrum or *Cladosporium* found on dead brown grass, some of the fungi causing "blueing" of wood pulp, and the two dissimilar but apparently related fungi which cause the majority of cases of chromoblastomycosis. If and when this relationship is more fully known it may be found necessary to make some revision in the nomenclature of the etiologic agents of chromoblastomycosis. Until further studies have been made in an effort to elucidate this problem, we do not see any advantage to be gained by a temporary revision.

#### APPLICABILITY OF THE NAME "CHROMOBLASTOMYCOSIS" TO THE DISEASE

Some discussion of the nomenclature of the disease is also necessary. Moore has proposed to change the name of the disease to "chromomycosis," because, as has been pointed out by many investigators, the fungus does not grow in the tissues by budding. The criticism is valid but the importance one attaches to it depends on how strictly the prefix "blasto" is defined. This prefix connotes a budding type of growth but in practice has been used loosely. In chromoblastomycosis the divergence from a yeastlike development is great. Septation of spherical or egg-shaped cells is frequent, and well developed hyphae may appear in the superficial crusts. True budding does not occur. In American blastomycosis the resemblance to yeasts is greater, but here too differences are apparent. *Blastomyces derma-*

titidis, the etiologic agent, is in culture a Hyphomycete with no resemblance to the yeasts. The parasitic phase in tissues presents the aspect of budding, but even here it does not look like a true yeast. Furthermore, one can find many cells which clearly represent abortive attempts to form hyphae. This characteristic is more easily interpreted when one studies the growth of this fungus on blood agar, on which it shows characteristics of both budding and hyphal growth. In short, both blastomycosis and chromoblastomycosis can be criticized as inappropriate names, since neither is caused by a true budding or yeastlike fungus. There seems to be little more reason for rejecting one than the other.

The disease was named chromoblastomycosis because of its resemblance to American blastomycosis, the prefix indicating that the etiologic agent was pigmented. There are further newly emphasized reasons for retaining the old name which expresses this relationship. It has been recently pointed out,<sup>6</sup> and it is again illustrated by the case we are reporting, that many cases of chromoblastomycosis, particularly those in temperate climates, bear a close clinical resemblance to blastomycosis. There is therefore, perhaps, more justification on these grounds for the name now than when it was first used. The criticisms listed here do not appear to us to be sufficient reason for changing the name, especially since it has not been a source of confusion.

#### OBJECTIONS TO THE NAME "CHROMOMYCOSIS"

There are definite objections to the name "chromomycosis." It focuses attention more sharply on the prefix and would indicate that the disease is one which is characterized primarily by pigment changes in the

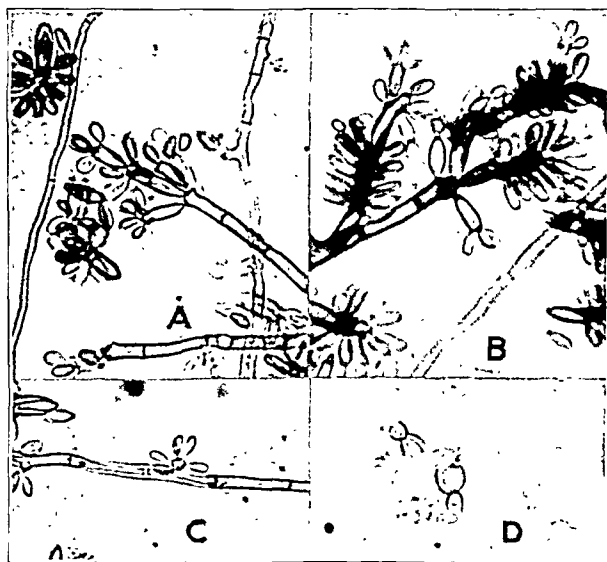


Fig. 5.—A and B, complex conidiophores combining different types of sporulation; C, knoblike conidiophores; D, phialophora type of sporulation in *Hormodendrum pedrosoi*.

infected tissues. Finally, the name is too nearly like the name chromophytosis (*tinea versicolor*), which is a fungous disease or group of related diseases characterized by just such pigment changes in the skin and is wholly unlike blastomycosis or chromoblastomycosis.

#### SUMMARY

In a case of chromoblastomycosis, the sixth reported from continental United States, the etiologic agent

13. Conant, N. F.: The Occurrence of a Human Pathogenic Fungus as a Saprophyte in Nature, *Mycologia* 29: 597-598, 1937.

was *Hormodendrum pedrosoi*. The case is interesting because of the early diagnosis (the case was of three months' duration), the unusual location of the lesion (wrist) and the apparently good response to potassium iodide therapy.

National Institute of Health—478 Peachtree Street.

#### ABSTRACT OF DISCUSSION

DR. JOSEPH GARDNER HOPKINS, New York: This seems more significant than the mere report of one conditional case of a rare disease, because cases of this disease, which Lane first described, have been cropping up more and more frequently of late. One suspects that it is probably more common than is realized. It is easy to see from the photograph which was presented that we may be missing cases which do not show the enormous warty growths that dermatologists are accustomed to think of as characteristic of the disease. This should stimulate us to be on the outlook for this condition in all our clinics. A second point of interest is the authors' treatment. The prognosis in chronic cases has seemed so bad that it does somewhat change our ideas to find a case that responded rather rapidly and apparently satisfactorily to therapy, although we do not know the later outcome. A third point that appealed to me in the report was the resistance of the authors to the temptation to change names. The thing that has done more to make mycology difficult and thereby has retarded its development has been the tendency to take well known fungi and fungous diseases and give them new names. It is that pernicious tendency which makes the literature of mycotic infections so extremely difficult to read intelligently and to evaluate at all.

DR. W. M. SAMS, Miami, Fla.: I had the opportunity of observing a case in Miami, as yet unreported. The lesion was on the left hand, was somewhat more verrucous than the photographs would indicate in the case reported by the authors. It was about the same size and was of more than twenty years' duration and yet had caused little or no difficulty. It responded to roentgen therapy and iodides with the greatest of ease. I saw the patient over a year ago but have not yet been able to find him again. This case did not originate in continental United States strictly speaking but occurred in a Nassau Negro, born in the Bahama Islands. He dates the onset of his trouble to an injury received when he struck his hand on a piece of wood or the gunwale of a boat about twenty years prior to the time at which I saw him.

DR. FRED D. WEIDMAN, Philadelphia: Our knowledge of this disease is rapidly increasing. Counting Dr. Sams's unreported case, it totals 7 for the United States; if we add Puerto Rico, the number is more than doubled. Practically all of this has occurred in the short space of seven years. In other words, it is the old story in medicine: namely, once we become aware of the possibilities of the presence of a condition and begin to look for it, we begin to find it. Dr. Pardo Castello recently sent me a list of 20 histologically proved cases that he had found in Havana in the last two years and a half! In short, there is a second hotbed of chromoblastomycosis in the world. The original and probably still the hottest one is in Brazil. There is thus a focus close to continental United States, namely, Cuba and Puerto Rico, which is significant in relation to Dr. Sams's case in Miami, and the authors' case from Atlanta. The original and supposedly typical clinical expression of the disease, namely those gigantic excrescences such as were seen on the screen on the leg of a patient, is not the type that is usually encountered in the United States. Perhaps we shall eventually be able to generalize to the effect that these lush examples of chromoblastomycosis are the kinds that are to be met in the tropics. In the United States only one of the 7 cases thus far reported has been of that type, namely the case of Wilson et al. in Fort Worth. All the others have been the simple types, but being simple they approach more closely the clinical picture of syphilis, tuberculosis verrucosa cutis, blastomycosis, frambesia, sometimes leprosy, dermatitis vegetans and a number of that sort. The diagnosis may be made easily. Scrapings and pus frequently

give immediate microscopic diagnosis by the potassium hydroxide technic, and the appearance of histologic sections is diagnostic even under the low power of the microscope. It is safe to predict that we are going to encounter increasing numbers of cases of chromoblastomycosis.

MORRIS MOORE, PH.D., St. Louis: Chromomycosis, as I prefer to call it, is so named because I find that the budding which is typical of blastomycosis is not found in this disease; instead one sees a "breaking off" of cells to form mulberry-like clusters, which is entirely different from the original conception of blastomycete formation. Chromomycosis was described for the first time in São Paulo, Brazil, by Pedroso, who called it a "black blastomycosis." In 1920, with Gomez, he published a series of 4 cases from Brazil, illustrating a number of clinical types involving the hands, feet and I believe one occurring on the neck. Recently a lesion of the face was described in a case from St. Louis. This lesion also was unusual in the sense that it seems to bring out the idea set forth by Dr. Conant that the organism is found in nature as a saprophyte on plants and wood. The patient had been a log handler for years. Ten years previously to his entry into our clinic he had burned his face with a match and perhaps the handling of logs brought out his infection in due course of time. I believe our patient has been fairly well cleared up, although he had some cerebrospinal symptoms which perhaps were not associated with his chromomycosis. We have not been able to contact him again. There are a number of organisms which may produce this disease. I have found all the fungous characteristics; that is, branching and the kind of cell formation typical of the *Hormodendrum*s, the cup formation of *Phialophora* and the *Acrotheca* type of "knotty stick" all in one genus. There are more than just *Hormodendrum pedrosoi* and *Phialophora verrucosa* as causative organisms in chromomycosis. In 1935 I published a paper in Argentina discussing the relationship and derivation of the various genera. On my return I received a reprint from Dr. Negroni of Buenos Aires with the inscription that because one of the genera failed to have a Latin description he had to describe a new genus. Consequently it may be concluded that, even though some writers may not be in accordance with me completely, the idea is prevalent that there are several different organisms. I still think, as all others have thought, that in due course of time we shall have a large number of cases really to explain this serious disease, because at times it is extremely serious with surgery the only course of treatment.

DR. HUGH HAILEY, Atlanta, Ga.: We are indebted to Dr. Emmons for his interest and his laboratory observations of this rare mycotic infection. From the clinical point of view, the lesion of this patient could not be differentiated from that of blastomycosis. The history of trauma three months prior to our inspection, the clinical appearance and the typical response to iodide therapy are observations which correspond with blastomycosis. It was only by means of laboratory studies that the correct diagnosis could be determined. On March 11, 1939, when I first saw the patient, the lesion was 4 cm. in diameter and had a definite verrucous and honeycombed margin from which purulent material could be expressed by gentle pressure. The proximal half of the margin was more elevated and more active than the distal half. The central depressed area was composed of smooth, reddened scar tissue. On March 25 the margin was smoother, less reddened and somewhat flattened. I saw the patient again on April 8, when it was noted that improvement continued. On April 28, inflammation had subsided markedly and the verrucous border had disappeared. His final visit was May 26, at which time the note was recorded that slight redness remained and that the margin was flattened and practically level with the surrounding normal skin. Post-inflammatory pigmentation was present. Our final report came from his daughter, relating his accidental death on July 4, also stating that the lesion was entirely healed. In our opinion the clinical cure was attained by iodides; roentgen rays were not an important adjunct to the treatment. We hope that this presentation will create more interest among fellow physicians in mycotic infections with the purpose of isolating more cases of this uncommon disease, for we feel that it is not so rare as the literature now reveals.

RADIATION IN THE TREATMENT OF  
CARCINOMA OF THE BODY OF  
THE UTERUS

A. N. ARNESON, M.D.

AND

HARRY HAUPTMAN, M.D.

ST. LOUIS

Analysis of clinical results obtained in carcinoma of the body of the uterus has revealed two factors of fundamental importance in the treatment of operable cases. The first is that hysterectomy alone is inadequate treat-



Fig. 1.—Uterus that received 4,000 mg. hours of radiation by an intra-uterine tandem applied one month before hysterectomy. Specimen from the museum of the Department of Gynecology, Washington University. Courtesy of Dr. W. C. Scrivner.

ment for certain types of clinically operable patients. The second point is that average results can be improved by combining radiation with surgery. Several authors have demonstrated a close relationship between microscopic appearance of tumor and end results. Collected statistics for hysterectomy alone given in an earlier publication show a greater percentage of five year cures among the well differentiated lesions than in the more anaplastic varieties.<sup>1</sup> More recent data presented by Scheffey and Thudium,<sup>2</sup> Ward and Sackett,<sup>3</sup> Healy and Brown<sup>4</sup> and others illustrate the importance of combining radiation with surgery in the attempt to improve clinical results, particularly among lesions of histologic types known to have a less favorable prognosis. For reasons not yet fully understood, preoperative irradiation is more effective than treatment administered after hysterectomy. One factor is the greater total dose that can be given by means of intra-uterine radium applied before removal of the uterus.

Read before the Section on Obstetrics and Gynecology at the Ninety-First Annual Session of the American Medical Association, New York, June 13, 1940.

From the Barnard Free Skin and Cancer Hospital and the Edward Mallinckrodt Institute of Radiology and Department of Obstetrics and Gynecology, Washington University School of Medicine.

1. Arneson, A. N.: Clinical Results and Histologic Changes Following the Radiation Treatment of Cancer of the Corpus Uteri, *Am. J. Roentgenol.* **36**: 461-476 (Oct.) 1936.

2. Scheffey, L. C., and Thudium, W. J.: Experience in Treatment of Carcinoma of Fundus Uteri with Five Year End Results in Forty-Seven Patients, *Am. J. Obst. & Gynec.* **35**: 1006-1019 (Dec.) 1937.

3. Ward, G. G., and Sackett, N. B.: Results of Radiation Therapy for Carcinoma of the Uterus at Woman's Hospital, New York, 1919-1932, *J. A. M. A.* **110**: 323-327 (Jan. 29) 1938.

4. Healy, W. P., and Brown, R. L.: Experience with Surgical and Radiation Therapy in Carcinoma of the Corpus Uteri, *Am. J. Obst. & Gynec.* **38**: 1-13 (July) 1939.

Owing to the excellent results obtained in the adult types of corpus cancer by surgery alone, there is a temptation to restrict the use of preoperative irradiation to the more undifferentiated lesions. A plan of that sort is founded on the belief that there are several different varieties of endometrial cancer. That such a variation exists clinically seems to be an established fact. There are, however, other factors that affect prognosis, such as the size of the uterus, the presence of infection and downward extension of the tumor into the cervix. An attempt to rely entirely on histologic features for individualization of treatment may entail an untoward risk for the patient. It is well known that some tumors may develop changes toward anaplasia and that others during treatment may undergo maturation toward a more adult type.<sup>5</sup> The possibility cannot be excluded that various histologic types merely represent different stages through which an individual lesion may pass.<sup>6</sup> A low grade tumor showing tendencies toward undifferentiation would certainly be expected to have clinical properties resembling lesions of a higher type. The question then arises as to whether undifferentiation is more apt to be the result of tumor age or the individual biologic properties of a given lesion. If anaplasia is more closely associated with the age of the tumor, a greater percentage of bulky and advanced lesions is to be expected among those types. Evidence that they tend to be more advanced is shown by the high incidence of recurrence following hysterectomy alone. It cannot be stated, however, whether the tendency to involve regions outside the volume of tissue removed at opera-

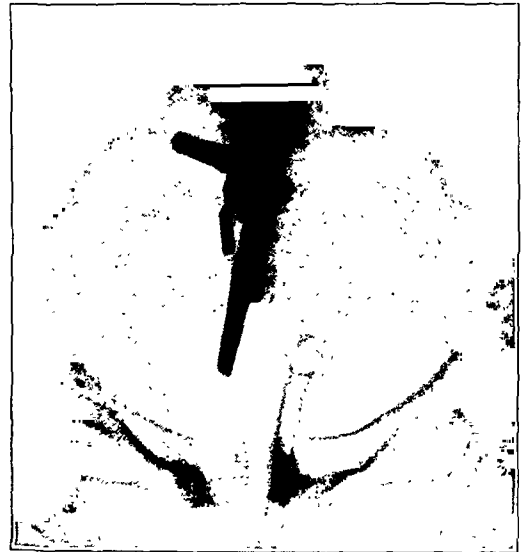


Fig. 2.—Intra-uterine tandem used in conjunction with multiple capsules of radium.

tion is the result of slow invasion of an old tumor or more rapid infiltration by a young lesion. Those questions may be of only academic interest but they raise an interesting problem for investigation. An attempt should be made to correlate gross appearance with microscopic features. Wide variations are to be expected, but undoubtedly there are small local lesions of the undifferentiated type. As far as clinical practice is concerned, however, it seems best to employ pre-

5. Arneson, A. N., and Stewart, F. W.: Clinical and Histologic Changes Produced in Carcinoma of the Cervix by Different Amounts of Roentgen Radiation, *Arch. Surg.* **31**: 542-567 (Oct.) 1935.

6. Teacher, J. H.: *A Manual of Obstetrical and Gynaecological Pathology*, edited by Alice J. Marshall, New York, Oxford University Press, 1935, p. 285.

operative irradiation in all operable cases rather than attempt to individualize the treatment on the basis of the biopsy specimen. It should be noted also that, in spite of variations in response to radiation shown by different types of corpus cancer, there seems to be no great justification at the present time for veering from the generally accepted belief that hysterectomy, whenever practical, remains the fundamental procedure.

Because of the relatively inaccessible location of the lesion, the radiation treatment of corpus cancer presents technical problems more difficult than those found in the cervix. The fundamental principles of irradiation, however, are exactly the same. In every instance the attempt must be made to deliver throughout the tumor-bearing region a dose believed to be adequate for control of the lesion in question. It is obvious that outlying tumor cells will receive lesser amounts than cells located nearer the irradiating sources. In the attempt to increase the dose reaching distant regions

radium source buried in tissue or in a body cavity there is an inner zone within which necrosis may occur and an outer zone receiving a dose adequate for the control of cancer. The respective volumes of tissue representing those zones varies with the dose employed as well as all other physical factors of the treatment. For a specified dose, differences in the two volumes might

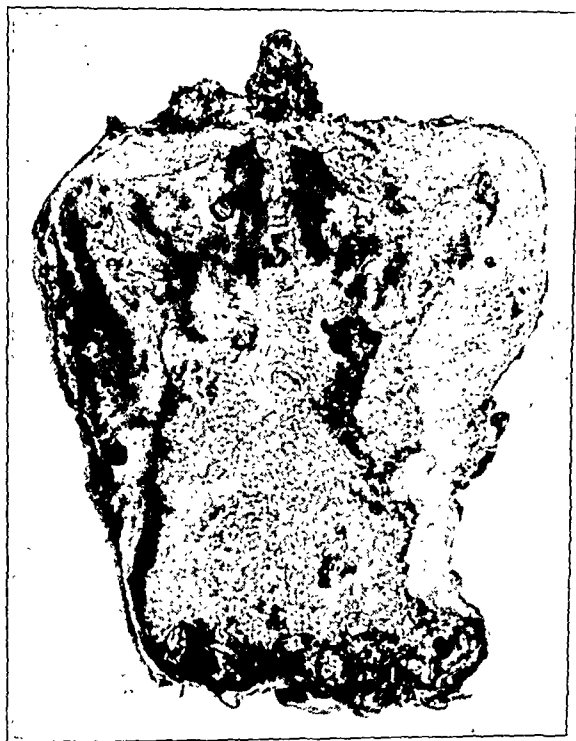


Fig. 3.—Uterus removed eight weeks after radium treatment shown roentgenographically in figure 2.

some of the more proximal points may be overtreated. This entails risk of both permanent damage to normal structures and extensive necrosis of tumor. Marked destruction of tissue by radiation with loss of integrity of the tumor bed not only results in complicating infection but also in interference with the orderly processes of regression. Such a breakdown in tissue may be followed by unrestrained growth of tumor.<sup>7</sup> It is essential that every effort be made to decrease the discrepancy between the minimum dose delivered to some regions and the maximum amount falling on other points. It is only by improvement in the distribution of radiation that the possibility for delivering an adequate dose throughout the tumor-bearing region can be increased with a minimum risk of radiation sequelae.

Variations in the distribution of radiation are more marked for radium than for x-rays. Surrounding every

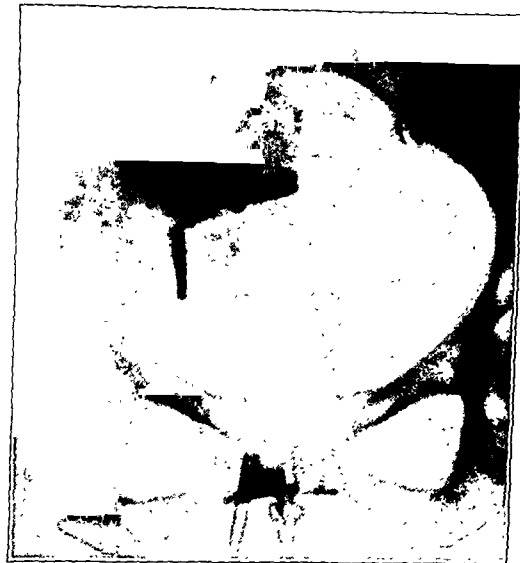


Fig. 4.—Distribution of radium obtained in a patient not treated with a tandem owing to absence of involvement of the cervical canal and the short length of the uterine cavity. Distortion of the uterus is due to excessive packing of the vagina.

be very slight in extremely radioresistant lesions with a low threshold for necrosis. Infection is one of the important factors believed to contribute to greater radioresistance of tumor cells and increased susceptibility of the tumor bed to necrosis.<sup>8</sup> In the treatment of cervix cancer the use of preliminary x-rays has proved of great value in the attempt to decrease pre-existing infection before the application of radium.<sup>9</sup>

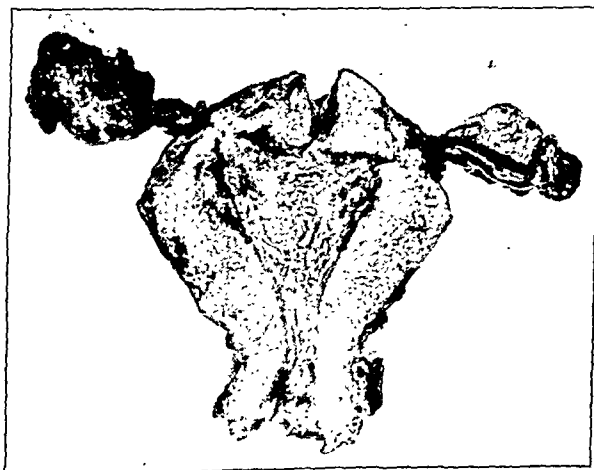


Fig. 5.—Uterus removed six weeks after radium treatment shown roentgenographically in figure 4.

The same procedure is equally effective in the treatment of corpus cancer. The decrease in infection obtained by a course of roentgen radiation lessens the

8. Arneson, A. N., and Hauptman, Harry: Radium Needles in the Treatment of Carcinoma of the Cervix and Vagina, *South. M. J.* 33: 286-293 (March) 1940.

9. Arneson, A. N.: Irradiation of Malignant Diseases of the Female Genitals, *Am. J. Obst. & Gynec.* 33: 893-901 (May) 1937.

7. Stewart, F. W.: Radiosensitivity of Tumors, *Arch. Surg.* 27: 979-1064 (Dec.) 1933.

risk of marked destruction of the tumor bed by intra-uterine radium. Furthermore, regression in the size of the lesion may facilitate the intra-uterine treatment of bulky tumors presenting technical difficulties interfering with a suitable application of radium. Finally, the dose contributed by x-rays, combined with that obtained from radium, increases the total volume of tissue receiving an adequate amount of radiation.

The intra-uterine applicator most frequently used in radium treatment of corpus cancer is a tandem of two or more capsules. In most instances the active length of the applicator extends from the level of the external os to the top of the fundus, with the sources in the uterine cavity containing greater amounts of radium than those in the cervical canal. There are two important objections to this method of treatment. In the first place radium applied by tandem may be located at distances from tumor that are enormous in relation to the rapid decrease in intensity occurring within a few millimeters of a given source. If the cavity is distorted by a bulky lesion or by a submucous myoma the tandem must be pushed to one side, so that considerable tissue may intervene between radium sources and some tumor cells. In cavities that are not distorted the radium may also fail to come in close contact with tumor in patients presenting small lesions located in one horn of the uterus. The second objection to a tandem is made on the basis of the distribution of radiation obtained from such a method of application. In the attempt to deliver an adequate dose to the entire uterus it is obvious that, as a result of the small number of sources employed, each single tube must contribute a relatively large amount of radiation. It is impossible, therefore, to prevent necrosis in tissues immediately adjacent to the tandem. Inadequacies of this method of treatment are shown in the photograph of the gross specimen given in figure 1. This patient, treated a few years ago, had a uterus slightly larger than normal with a bulky tumor in the fundus. Without preliminary x-rays, and one month before hysterectomy, she was given 4,000 mg. hours radiation by an intra-uterine tandem containing 100 mg. of radium. The upper portion held 75 mg., and 25 mg. was in the cervical end. The treatment not only failed to control the lesion but also resulted in considerable necrosis of tissue near the stronger part of the applicator.

One of the most practical methods for improving the distribution of radiation is the use of a greater number of irradiating sources.<sup>10</sup> By means of the contribution from each of the different tubes, the minimum tumor dose can be increased without employing any single source for an amount apt to result in extensive necrosis of adjacent tissue. The placing of multiple capsules inside the uterine cavity will also decrease the risk, noted for the tandem, of radium being too distant from all or portions of a corpus lesion. In the attempt to improve intra-uterine treatment several authors have devised special applicators. Some of these are described elsewhere,<sup>1</sup> and more recently Martin<sup>11</sup> has reported the use of small capsules of relatively low radium content attached by hinges to long wires so that they can be applied directly to the affected portion of the uterine cavity. Crossen<sup>12</sup> places one or more small capsules inside a rubber tube supported by a wire which can be sutured to hold the distributors at a given depth

and in a position preventing movement of sources in each lateral horn alongside an intra-uterine tandem. One of the most effective methods appears to be that devised by Heyman.<sup>13</sup> Capsules of a standard size containing small amounts of radium are introduced singly into the uterus until the cavity is completely filled.

A few years ago we began the use of a technic requiring a minimum of special apparatus in the attempt to devise a method not too elaborate to be found practical in most clinics. A method of that order must be one easily applied to a variety of lesions, including those presenting different degrees of distortion of the uterine cavity. The most logical procedure is the use of multiple capsules introduced singly into all available space in the attempt to obtain a satisfactory arrangement of radium that will correct the objections already made for a tandem. The various sources should be of a fairly uniform size and strength, each containing a small amount of radium. In many institutions, however, the number of relatively weak sources may be inadequate for all patients. Tubes containing greater amounts can be used if held inside an applicator or within a medium increasing the distance between radioactive material and the surface to which it is applied. By that means the intensity of radiation falling on the nearest tissue may be reduced to a rate approaching that obtained from weaker sources. The majority of clinics have a few tubes containing 25 mg. of radium or less, and lightly filtered needles of about 10 mg. strength are in fairly common use. It is a relatively simple matter to obtain capsules for holding those sources individually that will not only increase distance but also supply adequate filtration. If the uterus is not completely filled, however, and the application is checked by means of a roentgenogram taken while the radium is in place, it will be found that most of the sources invariably form an impaction in the lower uterine segment. This can be prevented if, during the insertion of radium, strips of narrow gauze are introduced to hold the tubes in place. Gauze employed in that manner also serves as a medium for increasing distances around capsules containing greater amounts of radium.

In applying radium to a given patient, the various capsules selected for treatment are first attached to a long and durable ligature. A single or double thickness of quarter inch gauze packing is folded over one of the stronger sources and introduced into the right or left cornu by means of uterine dressing forceps. The same procedure is carried out in the opposite horn, but the first gauze strip and ligature must be held firmly to prevent them from being pushed into the cavity. Weaker sources are reserved for central insertion in the attempt to deliver a more uniform distribution of radiation throughout the uterus. With the introduction of each additional radium capsule a small amount of gauze is pushed into the cavity from one of the two strips hanging from the external os. The cervical canal must be kept well dilated to insure safe and easy removal of all the sources. This can be done with packing or by placing the tube of greatest diameter at that point.

In the cervical canal and lowest portion of the uterine cavity it is usually impractical as well as unnecessary to place two or more capsules in parallel. A short tandem is well suited to the treatment of that region.

10. Arneson, A. N.: The Distribution of Radiation Within the Average Female Pelvis for Different Methods of Applying Radium to the Cervix, *Radiology* 27: 1-20 (July) 1936.

11. Martin, C. L.: Radiation Therapy in Carcinoma of the Fundus of the Uterus, *South. M. J.* 33: 135-143 (Feb.) 1940.

12. Crossen, H. S.: Personal communication to the authors.

13. Heyman, J.: Radiumhemmet Method of Treatment and Results in Cancer of the Corpus of the Uterus, *J. Obst. & Gynaec. Brit. Emp.* 43: 655-666 (Aug.) 1936.

It should be noted, however, that among patients with deep cavities, or in those with downward extension of the lesion into the cervix, the dose per centimeter tandem length must in most instances be greater than that which would be obtained from a tandem composed of capsules of the same strength as those used higher up in the uterus. As an example of such an instance may be cited a patient presenting a cavity more than 4 inches deep with evidence at curettement of involvement extending into the cervical canal. Following a preliminary course of x-rays, seven capsules of 10 mg. each (two were of smaller size than the others) were packed into the upper uterus. A tandem about 5 cm. long containing two tubes of 25 mg. each was inserted into the cervical canal. A roentgenogram made during treatment is shown in figure 2. It can be seen that the various sources are fairly well separated by gauze and extend out into each horn, but at the middle of the uterus there may be an unnecessary congestion of radium. The patient received approximately 5,800 mg. hours of radiation. Each of the separate capsules had an active length of about 2 cm. and delivered 480 mg. hours. The dose from the tandem was about 480 mg. hours per centimeter of length.

Eight weeks after radium treatment the uterus was removed. A photograph of the gross specimen opened along the right lateral border and across the top of the fundus is shown in figure 3. There was considerable

*Average Number of Capsules and Total Doses of Radiation Employed in Uterine Cavities of Different Lengths*

Total Number of Patients	Average Depth Cavity, Inches	Average Number of Sources	Average Total Dose, Mg. Hrs.	Average Dose per Source, Mg. Hrs.
8	3 to 4	6	4,800	800
7	4 to 5	8	5,600	700
3	5 to 6	9	6,100	675

necrosis and ulceration involving the cervical canal and lower portion of the uterine cavity. The distribution of this reaction seemed to correspond roughly to the location of the tumor. There was less destruction of tissue in the fundus, but all of the endometrium in that region showed marked evidence of radiation effect with an accompanying inflammatory exudate. Microscopic study of sections cut from various regions of the uterus showed persistent but markedly degenerated tumor in some areas. It is impossible to state whether cells showing such marked degeneration eight weeks after radium treatment might recuperate to form actively growing and fully viable cancer. At the same time the persistence of recognizable tumor illustrates the importance of following irradiation with hysterectomy.

In this case it is difficult to explain either the gross variations in tissue damage or the survival of cancer in areas showing the greatest destruction. It is true that both of those phenomena were noted chiefly in a region believed to correspond to the location of the primary lesion. As far as injury to tissues is concerned, one might expect radiation to produce a greater effect in the tumor area than in the fundus which was relatively free from involvement. At the same time the difference in degree of damage occurring in the two poles of the uterus is greater than that which would be expected for a reasonably uniform distribution of radiation. It cannot be explained on the basis of overtreatment of the lower region, however, because necrosis extended over an area greater than the length of the

tandem. Careful examination of the roentgenogram and all physical factors of the treatment indicates that only in the region about the upper end of the tandem was there risk of delivering an excessive dose. Furthermore, the marked evidence of effect of radiation in uninvolved endometrium lining the fundus indicates that the upper part of the uterus received a large dose despite the absence of necrosis. It would appear that in this tumor factors were present which tended to increase the radioresistance of cancer cells and lower the threshold for necrosis. Before treatment there was clinical and histologic evidence that the lesion was badly infected and ulcerated.

Preoperative irradiation may result in complete disappearance of tumor without necrosis. In such instances, however, the lesions tend to be smaller with less evidence of infection and ulceration. In figure 4 is shown the distribution of radium obtained in a case in which there was a cavity 3 inches deep. The use of a tandem was not deemed essential, owing to the lesser depth of the cavity and the absence of involvement of the cervical canal. Seven tubes containing 10 mg. of radium each were packed into the uterus with one of the capsules resting in the cervical canal.<sup>14</sup> The total dose was 3,500 mg. hours of radiation. Treatment was given with the same sources used in the first case. Each capsule had an active length of about 2 cm., and the dose per radium tube was essentially the same in the two instances. In the first case it was 480 mg. hours per source and in the second it was 500 mg. hours of radiation. Hysterectomy was performed six weeks after radium treatment in the last case. The reproduction of a photograph of the gross specimen is shown in figure 5. There was no deep necrosis of tissue, but all of the endometrium showed marked evidence of radiation effect including the usual inflammatory exudate. Within the cervical canal, however, the reaction was of a lesser degree. No residual tumor was found in the examination of sections removed from various parts of the uterus.

Explanation of the difference in response to irradiation shown in the cases discussed would seem to be found in the biologic properties of the two lesions rather than in the physical factors of treatment. It has already been pointed out that the dose delivered by each radium source was essentially the same in the two instances. The two uteri also received about the same tumor dose despite the fact that the total number of milligram hours of radiation in one was considerably greater than in the other. In the attempt to deliver a comparable tumor dose to all patients, it is obvious that the total amount of radiation and the number of sources used in treatment must vary with the size of the cavity and the tumor-bearing region. In the table are given averages for the number of capsules and total doses used in cases presenting cavities of different depths treated prior to 1940. It can be seen that the values given for the average dose per radium source are high in comparison with those used in the two cases described. Values for the number of capsules employed in treatment appear to be low. Those differences are due to the more frequent use of a smaller number of stronger sources among the first patients treated with multiple capsules. It should be noted, however, that the average dose per source decreases

14. In the roentgenogram one source of radium cannot be visualized. Angulation in the shape of the uterus is due to excessive packing of the vagina. In this case the cervical canal was kept well dilated with gauze. A better procedure would have been the use of a capsule of greater diameter in that region.



with the use of a greater number of tubes in the larger uteri receiving greater total amounts of radiation. That factor is of considerable importance and must be taken into account in planning the treatment of each patient.

The physical factors of radium treatment are very complex, and it must be admitted that sources of various size and strength have been used at different and sometimes unknown distances without any attempt being made to calculate tissue doses. It is obvious, therefore, that no high degree of accuracy has been attained in the attempt to deliver comparable amounts to all patients. Neither can it be said that the distribution of radiation has been satisfactory in every instance. Complete filling of the uterine cavity with capsules of the same length, diameter, filter and strength would standardize many of the physical factors of treatment. Even by that means, however, there would be variations in the dose delivered throughout the tumor-bearing region as the result of irregularities in the arrangement of radium with variations in the shape of the cavity in different cases. The fact remains, nevertheless, that any attempt to increase the number of sources used in treatment will improve the distribution of radiation. Among the eighteen patients in our series there was less variation in the minimum tumor dose each received than in the maximum amounts arriving at points nearer the irradiating sources. In every instance the minimum tumor dose was greater than that which could have been obtained from a tandem alone. It is also reasonable to believe that, for the control of tumor within a given volume of tissue, there was a lesser amount of necrosis following the use of multiple capsules. The method has proved to be one easily applied to all patients, and it is not too elaborate to be found practical in most clinics.

#### SUMMARY AND CONCLUSIONS

Analysis of statistics reported for corpus cancer shows that the best results are obtained from preoperative irradiation followed by hysterectomy. In radium treatment there are definite limitations to the use of an intra-uterine tandem alone. A method for using multiple capsules in the attempt to improve the distribution of radiation has proved to be one easily applied to all patients and not too elaborate for practical use in most clinics. There is evidence that infection is one of the factors contributing to increased radioresistance of cancer cells and to increase in the risk of necrosis following irradiation. In the attempt to lessen the amount of preexisting infection a preliminary course of x-rays should be used before the insertion of intra-uterine radium.

#### ABSTRACT OF DISCUSSION

DR. WILLIAM P. HEALY, New York: The authors describe a plan of intra-uterine distribution of radiation by means of multiple radium capsules in order to increase the distribution of radium throughout the cancer-bearing field in the uterus. It must be borne in mind that the cancer-bearing uterus is not a hollow structure like a balloon. It is an irregular cavity with tumor tissue projecting into it from one side or all sides or the top side, and it is a difficult matter in the majority of cases not to traumatize the interior of the uterus with foreign bodies. I have felt that about as efficient irradiation of the entire uterine cavity is obtained over an area 2.5 cm. distant from the central part of the cavity with the simple tandem applicator or multiple capsule in line as in a string, as with multiple foci pushed off to the sides. On the other hand, if the uterus is large and the entire carcinoma-bearing area cannot

be irradiated in one treatment, I think then the Heyman (Stockholm) plan is better; in other words, divided treatments with capsules in line, three or four, to go from the external os to the dome of the fundus, and treatments given not closer than four weeks to one another. If one wants to give a total of 4,800 mg. hours, that should be divided into three treatments of 1,600 mg. each one month apart. The uterus will contract down between the individual treatments and satisfactory irradiation will be obtained in that manner. In addition, if one is dealing with a case in which there is a good deal of infection, it is the better plan to give small repeated doses at intervals. My associates and I have made 3,600 mg. hours with a tandem or a string of three capsules our minimum dosage if we are going to treat the patient with only a single dose preliminary to a hysterectomy. There are two types of corpus cancer histologically. One is amenable to cure by hysterectomy alone; the other, more malignant, requires preliminary irradiation plus hysterectomy. If the uterus is larger than a two and a half months gestation in size, we have found that the prognosis is bad with irradiation alone. If the uterus is smaller than a two and a half months gestation and the patient is a poor surgical risk, one can be reasonably sure of getting about 40 to 45 per cent five year cures with irradiation alone. In the larger uterus, therefore, regardless of the fact that the patient may be a bad risk, unless she has metastases I strongly urge hysterectomy.

DR. A. N. ARNESON, St. Louis: It is obvious that no single method of treatment can be applied to all patients. In the attempt to improve clinical results it is essential to individualize the treatment of each patient. The use of multiple capsules of radium presents a reasonably flexible technic for irradiating corpus cancer, which, in the most favorable circumstance, is a relatively difficult procedure. Further advance in methods of treatment may result in the administration of doses adequate for complete destruction of tumor in a greater percentage of cases. Gynecologists have at their disposal an opportunity for important clinical and laboratory studies. Careful observations on patients and on specimens removed after preoperative irradiation may contribute valuable data on the biologic properties of corpus lesions. It is also possible that knowledge obtained in that manner may be applied to other types of cancer.

#### SUPPRESSION OF LACTATION BY TESTOSTERONE

PAUL V. DUFFY, M.D.

AND

JOSEPH CORSARO, M.D.

CLEVELAND

Suppression of lactation in the puerperal breast frequently is desirable or necessary. After premature or still births, toxemia of pregnancy and some cesarean sections, when there is malformation or abscess of the breast or cracked nipples and in the presence of certain constitutional diseases, such as tuberculosis, diabetes and heart disease, there is valid reason to prohibit lactation. The measures employed for this purpose, until recently, were empiric and generally consisted of application of tight breast binders, with camphor liniment or belladonna unctions, restriction of fluids, saline purges and numerous other procedures of questionable value.

Kurzrok and O'Connell<sup>1</sup> first demonstrated that it is possible to inhibit lactation in women by administering androgen in the form of testosterone propionate. They reported successful results in 19 of 21 cases.

Birnberg, Kurzrok and Klor<sup>2</sup> later reported using testosterone propionate to inhibit lactation in a series

1. Kurzrok, Raphael, and O'Connell, C. P.: Inhibition of Lactation During Puerperium by Testosterone Propionate, *Endocrinology* 23: 476-478 (Oct.) 1938.

2. Birnberg, C. H.; Kurzrok, Lawrence, and Klor, S. J.: Inhibition of Lactation During Puerperium by Testosterone Propionate, *Am. J. Obst. & Gynec.* 39: 107-109 (Jan.) 1940.



of 56 cases, with successful results in 45. In 2 cases they gave doses of 100 mg. on the day of delivery, with complete inhibition of lactation.

TABLE 1.—Cases in Which Suppression of Lactation Was Secured with Testosterone Propionate

Case	Day Post Partum	Condition of Breast	Dose, Mg.	Observations
1	3d	Engorged	5	Relief in 12 hours
	4th	.....	5	Breasts slightly tender
	5th	.....	5	Breasts soft, not tender
2	4th	Engorged, tender	25	Definite relief in 12 hours
	5th	.....	10	Breasts softer
	6th	.....	10	Breasts soft, not tender
3	3d	Moderately engorged	10	Relief in 12 hours
	4th	.....	10	No pain or tenderness, 24 hours
4	4th	Markedly engorged and painful	10	Relief in 2 hours
	5th	.....	10	Soft, not tender in 24 hours
5	4th	Engorged and painful	5	Relief in 12 hours
	5th	.....	10	Breasts soft, not tender
	6th	.....	5	Soft, slight secretion
6	3d	Engorged and painful	10	Definite relief in 2 hours
	4th	.....	10	Breasts softer
	5th	.....	10	Breasts soft; no secretion
7	3d	Engorged and tender	10	Some relief in 4 hours
	4th	.....	10	Breasts firm; moderately tender
	5th	.....	10	Definite relief
	6th	.....	10	Breasts soft, no secretion
8	3d	Engorged and tender	25	Marked decrease in tenderness in 12 hours; no tenderness in 24 hours
			25 (8 hr. later)	
9	4th	Engorged and painful	25	Complete disappearance of pain and tenderness in 3 hours; breasts soft, not tender in 24 hours
			25 (8 hr. later)	
10	2d	Engorged	25	Relief in 12 hours but continued engorgement
	3d	.....	25	Less engorgement
	4th	.....	..	Breasts soft, no tenderness
11	4th	Engorged and painful	25	Relief in 12 hours
	5th	.....	25	Soft, not tender; suppression of secretion
12	3d	Engorged and very tender	25	Relief in 4 hours
	4th	.....	25	Soft, not tender; no secretion
13	3d	Engorged and very tender	25	Relief in 6 hours
	4th	.....	25	Soft, not tender; no secretion
14	4th	Engorged and very tender	25	Relief in 6 hours
	5th	.....	25	Soft, not tender; no secretion
15	3d	Beginning engorgement	25	Continued engorgement and tenderness for 12 hours
	4th	.....	25	Soft, not tender; no secretion in 24 hours
16	3d	Moderately engorged	25	Definite relief in 12 hours
	4th	.....	25	Slight tenderness for 24 hours
	5th	.....	25	Soft, not tender; slight secretion on 8th day
17	3d	Engorged and very tender	25	Relief in 6 hours, but persistent engorgement
	4th	.....	25	Decreased engorgement in 24 hours; complete relief in 48 hours; breasts soft, not tender; no secretion
18	5th	Tender, slight engorgement, slight secretion	25	Complete relief of tenderness and engorgement in 12 hours; breast soft, slight secretion
	6th	.....	25	Breast soft, no secretion

Siegler and Silverstein<sup>3</sup> reported that in 50 cases lactation was suppressed successfully in 47 instances. They observed that pain in the breast due to congestion was the first symptom to disappear. They obtained uniformly good results with doses of 125 to 150 mg. These doses were higher than those employed by Kurzrok and O'Connell and much higher than was necessary in the cases we have studied.

3. Siegler, S. L., and Silverstein, L. M.: Use of Testosterone Propionate in Inhibition of Lactation During Puerperium, *Am. J. Obst. & Gynec.* 29: 109-112 (Jan.) 1940.

## CLINICAL RESULTS

**Testosterone Propionate.**—The effect of testosterone propionate<sup>4</sup> has been studied in a series of 25 cases, which have been grouped according to the functional status of the breasts. In the first, and largest, group, of 18 cases (table 1) the breasts were definitely engorged, tender and painful, and the administration of the testosterone propionate was begun on the third or fourth day post partum. The dosage was varied to determine, if possible, the minimum dose necessary to relieve the mammary engorgement and to suppress lactation. The doses ranged from 15 to 75 mg., with the largest quantity given at a single injection, 25 mg. The injection was repeated usually in twenty-four hours, but in 2 cases it was repeated in one hour and in 2 cases in eight hours. The tenderness and engorgement of the breasts were relieved promptly, sometimes dramatically, and in all cases lactation was suppressed within twenty-four to forty-eight hours.

In table 2 are shown the details in 4 cases in which lactation had been definitely established for variable periods. Doses which proved entirely effective in the cases shown in table 1 were injected at intervals of twenty-four hours, without appreciable effect in suppressing lactation.

In addition to the cases shown in tables 1 and 2, there were 3 cases in which 25 mg. of testosterone propionate was administered on the first day post partum, with repetition of the dose on the second and third days. The treatment failed in all 3 cases, and engorgement of the breasts occurred on the third to the sixth day after delivery.

Testosterone propionate also is useful clinically in relieving the pain and tenderness of engorged breasts in cases in which there is no desire to suppress lactation. Small doses (5 to 10 mg.) may be injected, and if nursing is continued at regular intervals lactation will continue with no evidence of diminished secretion.

**Methyl Testosterone.**—Although testosterone propionate injected subcutaneously was used in all the cases reported here, in a subsequent series of cases it has been found that methyl testosterone given orally in doses of 25 mg. at intervals of four hours or three times a day for six doses produces results comparable to those obtained with 50 to 75 mg. of testosterone propionate administered subcutaneously.

## COMMENT

Our experience in 25 clinical cases would seem to indicate that the time at which the testosterone is administered distinctly affects the results of treatment. A dose of 50 to 75 mg. of testosterone propionate was effective in relieving mammary engorgement and in suppressing lactation in all cases in which it was administered at the beginning of lactation, that is, on the third or fourth day after delivery. When similar quantities were injected immediately post partum or after lactation had been established for some time, they were ineffectual.

The reason for the aforementioned results becomes clear in the light of facts that are known about the physiology of lactation and the effects of the male sex factor represented in testosterone propionate.

Throughout active sex life there are cyclic changes in the breasts produced by the influence of ovarian hormones.<sup>5</sup> In the postmenstrual phase there is a

4. The product used was oreton, furnished by the Schering Corporation.  
5. Procter, I. M.; Carpenter, C. C., and Morehead, R. P.: The Relation of Chronic Cystic Mastitis to Malignancy, *Surg., Gynec. & Obst.* 70: 671-678 (March) 1940.

regressive change, in which the epithelium becomes quiescent and the connective tissue is active. After ovulation, when the corpus luteum forms, the breast enters a proliferative stage. The stroma softens and the epithelium becomes active; secretion appears in many of the ducts and distends them to produce the swollen, tender premenstrual breasts. These changes are in preparation for pregnancy and parallel the response of the endometrium to the ovarian hormones. When pregnancy ensues, one of the earliest maternal changes is the increasing fullness and tenderness of the breasts. Under the influence of the persistent corpus luteum the epithelium of the breast continues its activity at the expense of the connective tissue. Many new acini are formed from the budding ducts, and fat is replaced by the abundant epithelial tissue.

Hildebrandt<sup>6</sup> has suggested that the placenta elaborates a substance which stimulates the growth of the mammary gland and at the same time inhibits lactation. Werner<sup>7</sup> expressed the belief that the ovarian hormones which are present in unusual quantities during pregnancy produce mammary proliferation but inhibit the action of the anterior pituitary lactogenic hormone. With Collier,<sup>8</sup> he found that activity of the breasts occurred in 13 castrated girls treated with estrone (theelin).

After delivery there is a rapid withdrawal of the ovarian estrogenic factors, which act as inhibitors of the hypophysis. Freed from these inhibiting factors, the anterior lobe of the pituitary gland produces prolactin (Riddle), which stimulates the secretion of the mammary ducts and initiates lactation, usually about forty-eight hours after delivery.

The continuation of lactation is dependent on peripheral stimulation or suckling, as has been shown by the work of Selye.<sup>9</sup> He cut the main galactophore at each of the nipples of 7 lactating rats. The mothers were returned to their litters, and since none of the nipples yielded milk the young nursed them all to the same extent. In a control series, the litters were removed from 10 rats on the third day of lactation. All animals were killed three to fourteen days after the beginning of the experiment. In the first group, in which the milk ducts were cut, the mammary glands were turgid with large quantities of milk even on the fourteenth day, while in the control group the glands contained no milk after three to five days and the alveoli began to disappear after the sixth to the eighth day.

In view of the foregoing facts, it is easy to explain the results reported in our clinical cases. The testosterone propionate in the doses employed was effective in suppressing lactation only when the estrogenic factors which inhibit mammary secretion during pregnancy had ceased to function and before regular lactation had been established through the stimulation afforded by suckling. The influence of such stimulation would account for the failure of treatment to suppress lactation in the 4 cases recorded in table 2, in which lactation had been well established by nursing for a considerable period. The failure in 3 additional cases, in which moderate doses of testosterone were administered immediately post partum, can be explained by the fact that in these

quantities the testosterone probably was eliminated by excretion by the time the pituitary-inhibiting factors of the ovarian hormones had been removed from the circulation and hence was not present in sufficient quantity to inhibit the onset of secretion.

Our failure to suppress lactation by administering testosterone immediately post partum, as contrasted with the success reported by Birnberg, Kurzrok and Klor<sup>2</sup> in 2 cases in which they administered 100 mg. on the day of delivery, may thus be accounted for in the light of experiments performed by McCullagh, Rumsey and Cuyler.<sup>10</sup> They found that when testosterone propionate was injected into males with hypogonadism the urinary androgens rose in proportion to the dose. After a single moderate dose the increased secretion lasted for only twenty-four hours, while larger doses effected an increase for several days. This prolonged effect of larger doses probably would account for Birnberg's<sup>2</sup> findings.

In normal males, McCullagh and his co-workers<sup>10</sup> found that the injection of testosterone propionate

TABLE 2.—Cases in Which Testosterone Propionate Failed to Produce Suppression of Lactation

Case	Day Post Partum	Condition of Breast	Dose, Mg.	Observations
1	8th	Secreting	25	Slight lessening of secretion
	9th	.....	25	Continued secretion
	10th	.....	25	Some reduction, but not suppression of secretion
2	60th	Secreting	10	Slight lessening of secretion
	61st	Engorged	10	Marked engorgement of breast in 24 hours; lactation continued but was definitely decreased
3	61st	Secreting	10	No change
	62d	.....	10	No change
	63d	.....	10	Continued to lactate
4	5th	Secreting and tender	25	Disappearance of tenderness in 6 hours; secretion continuing at end of 24 hours
	6th	.....	25	No change in secretion
	10th	.....	..	Definite diminution in secretion but lactation continued; breasts much softer and not so full

caused a prompt increase in the excretion of androgenic material. This was followed by a period of subnormal androgenic excretion, with return to normal after a few days. They expressed the belief that this period of subnormal excretion probably represents a period of pituitary depression caused by the injection of testosterone.

It would appear, then, from our studies and the other clinical work reported that the pituitary depression caused by moderate doses of testosterone administered at the initiation of the secretory phase of the breasts is sufficient to inhibit the lactogenic function of the pituitary gland and to suppress lactation.

#### SUMMARY AND CONCLUSIONS

In 18 of 25 cases in which the preparation was administered at the beginning of lactation (approximately forty-eight hours after delivery), a dose of 50 to 75 mg. was effective in all instances. Similar quantities of testosterone were not effective in suppressing lactation in 4 cases in which lactation was definitely established when treatment was begun and in 3 cases in which testosterone was administered immediately after delivery.

6. Hildebrandt, P.: Zur Lehre von der Milchbildung, Beitr. z. chem. Physiol. u. Path. 5: 463-475, 1904.

7. Werner, A. A.: Lactogenic Hormone: Severe Reactions from Its Use. Endocrinology 24: 119-121 (Jan.) 1939.

8. Werner, A. A., and Collier, W. D.: Effect of Theelin Injections on Castrated Woman with Histologic Report, J. A. M. A. 100: 633-640 (March 4) 1933.

9. Selye, Hans: Nervous Control of Lactation, Am. J. Physiol. 107: 535-538 (March) 1934.

10. McCullagh, E. P.; Rumsey, J. M., and Cuyler, W. K.: Excretion of Urinary Androgens Following Injection of Testosterone Propionate, Endocrinology 24: 833-837 (June) 1939.

From these findings it may be concluded that testosterone propionate administered subcutaneously in quantities of 50 to 75 mg. over a period of two to three days at the initiation of the secretory function of the breast is effective in suppressing lactation.

Smaller doses (5 to 10 mg.) may be administered to relieve the pain and tenderness in the engorged breast without diminution of secretion provided nursing is continued at regular intervals.

Methyl testosterone administered by mouth in doses of 25 mg. at intervals of four hours for six doses produces results comparable to those obtained with 50 to 75 mg. of testosterone propionate administered subcutaneously.

Carnegie Medical Building.

## NEPHRITIS IN SCARLET FEVER AND ITS TREATMENT

CONRAD WESSELHOEFT, M.D.

BOSTON

During the eruptive phase of scarlet fever the urine rarely shows more than a trace of albumin, a few granular casts and possibly a few leukocytes and red cells. This relatively mild inflammation of the kidneys usually subsides with the rash and fever and requires no treatment other than that generally applicable to the disease itself. The fact that this initial renal inflammation responds to the early use of scarlet fever antitoxin is evidence of its being due to the direct action of the erythrogenic toxin.<sup>1</sup>

Glomerulonephritis may occur during the eruptive stage, but the great majority of severe cases take place late in the convalescence<sup>2</sup> and often when the initial rash and fever have been so extremely mild<sup>3</sup> as to be without any signs of the benign renal disturbance which I have just mentioned.<sup>4</sup>

It is impossible to consider here the physiologic mechanism of the origin of glomerulonephritis in scarlet fever and the many theories which have been expounded with regard to it. However, it is worthy of mention that indirect evidence has been accumulating in support of the idea that an intense antigen-antibody reaction is connected with the origin of glomerulonephritis in this disease.<sup>5</sup> We must confine ourselves here to a few pertinent observations.

Lyttle<sup>6</sup> found that the Addis sediment count of the urine was increased during the convalescent stage in fourteen cases

of scarlet fever, yet the normal count showed wide variations.<sup>7</sup> In a study of 202 children convalescing from scarlet fever, Calvin and Carbone<sup>8</sup> found a positive orthotolidine test in ninety-nine, or 44 per cent. These observations suggest that some degree of inflammation is frequently present during the late stage of scarlet fever. In line with this is the finding of positive nephrotoxic serum reactions in 92 per cent of scarlet fever patients studied by Schwenker and Comploier.<sup>9</sup>

Gunn and Griffith<sup>10</sup> found that one group ("type 2") of scarlet fever streptococci in the nose and throat cultures was particularly apt to be associated with nephritis, but the series studied consisted of only 100 cases, and this observation has not been confirmed or refuted by further studies. Streptococci are but rarely found in the urine<sup>11</sup> or in the blood<sup>12</sup> during the acute glomerulonephritis. In a case of severe acute hemorrhagic nephritis arising on the thirteenth day and complicated with bacteremia, Chapman used chemotherapy effectively along with other measures to bring about recovery.<sup>13</sup> The routine use of sulfanilamide in scarlet fever does not induce nephritis.<sup>14</sup> However, this drug and its allied compounds may be precipitated in the renal pelvis and give rise to hematuria.

Lichtenstein<sup>15</sup> found nephritis more common in cases treated in the open ward than in those cared for in strictly isolated cubicles. This finding conformed to the increased incidence of other complications in the open ward. Nephritis is less common in the warmer months of the year when there are less of those mixed infections which predispose to activation of residual streptococci. It is most common in childhood and in later life.<sup>16</sup> A strong family predisposition has been demonstrated in certain epidemics studied in this respect.<sup>17</sup>

The onset, indicating severe renal damage, may be gradual, yet it may be without warning in the routine urinalysis of the previous day. In its "explosive character"<sup>18</sup> the onset resembles that of purpura hemorrhagica, a more rare but at times an equally serious complication of the convalescent stage.<sup>19</sup> The latter phenomenon is purely a vascular one, but we must not lose sight of the fact that the nephritis, both in its early and in its late forms, is associated with local and remote vascular disturbances.<sup>20</sup> The onset of the renal symptoms frequently coincides with a renewed activity of the streptococcus in the throat, cervical lymph glands, sinuses, middle ear or mastoid.

The relationship of these septic foci to glomerulonephritis has been the subject of much speculation. Suffice it to say that glomerulonephritis may occur in the absence of any evidence that a septic focus exists. On the other hand, Friedemann<sup>21</sup> reports three cases

7. Snoke, A. W.: The Normal Addis Sediment Count in Children, *J. Pediat.* **12**: 473 (April) 1938.

8. Calvin, Joseph K., and Carbone, Joseph: Erythrocytes in Urinary Sediment in Health and in Disease (Scarlet Fever): Studies by the Orthotolidine Test, *Am. J. Dis. Child.* **57**: 1035 (May) 1939.

9. Schwenker, F. F., and Comploier, F. C.: The Production of Kidney Antibodies by Injection of Homologous Kidney Plus Bacterial Toxins, *J. Exper. Med.* **70**: 223 (Sept.) 1939.

10. Gunn, W., and Griffith, F.: Bacteriological and Clinical Study of One Hundred Cases of Scarlet Fever, *J. Hyg.* **28**: 250 (Dec.) 1928.

11. Friedemann, U., and Deicher, H.: Weitere klinische und experimentelle Untersuchungen über den Scharlach, *Ztschr. f. klin. Med.* **108**: 737, 1928. Longcope.<sup>2</sup> Peters.<sup>20</sup>

12. Longcope.<sup>2</sup> Peters.<sup>20</sup>

13. Chapman, A. W.: The Treatment of the Bacteremia of Post-scarlatinal Nephritis with Prontosil and Prontylin, *Arch. Pediat.* **55**: 560 (Sept.) 1938.

14. Wesselhoeft, Conrad, and Smith, Edward C.: The Use of Sulfanilamide in Scarlet Fever, *New England J. Med.* **219**: 947 (Nov. 5) 1938.

15. Lichtenstein, A.: Studies in Scarlet Fever: IX. A Note on the Effect of Individual Isolation on the Course and Complications of Scarlet Fever, *Acta paediat.* **12**: 95, 1931.

16. Weaver, G. H., in Abt, I. A.: *Pediatrics*, Philadelphia, W. B. Saunders Company, 1925, vol. 6, p. 338.

17. Escherich, Theodor, and Schick, Béla: *Scharlach*, Vienna, 1912, pp. 118-119.

18. Pospischill, Dionys, and Weiss, Fritz: *Ueber Scharlach* (der Scharlachkrankung), Berlin, S. Karger, 1911, p. 137.

19. Box, C. R.: Complications of the Specific Fevers: Lumleian Lectures, *Lancet* **1**: 1217 (June) 1933. Gibson, A. G., and Hobson, F. G.: Hemorrhagic Purpura Following Scarlet Fever: Report of Two Cases in One Family, *ibid.* **1**: 509 (March 5) 1932.

20. Peters, J. P.: Some Factors in the Etiology of Bright's Disease, *New England J. Med.* **213**: 653 (Oct. 3) 1935.

21. Friedemann, U.: Das Scharlachproblem, *Klin. Wchnschr.* **7**: 2277 (Nov. 25) 1928.

From the Haynes Memorial, Massachusetts Memorial Hospitals, and the Department of Pediatrics, Harvard Medical School.

Read in the panel discussion on Some Contagious Diseases before the Section on Pediatrics at the Ninety-First Annual Session of the American Medical Association, New York, June 13, 1940.

1. Dick, G. F., and Dick, Gladys H.: *Scarlet Fever*, Chicago, Year Book Publishers, Inc., 1938, p. 44.

2. Longcope, W. T.: The Pathogenesis of Glomerular Nephritis, *Bull. Johns Hopkins Hosp.* **45**: 335 (Dec.) 1929. Weaver.<sup>16</sup> Neu.<sup>4</sup>

3. The late appearance of a glomerulonephritis may occur in individuals immune to the toxin who show merely a sore throat but no rash, or it may follow equally late after the tonsillitis due to nonscarlatinal strains. Glomerulonephritis has been subdivided into acute focal glomerulonephritis of bacteremic origin and acute diffuse glomerulonephritis (Longcope<sup>2</sup>), the postinfectious form encountered late in the convalescence of scarlet fever. The clinical differentiation of these forms is sometimes impossible, especially as they may be in combination. Furthermore, the treatment remains symptomatic in both.

4. Neu, Walther: Klinischer Beitrag zu den Nierenerkrankungen bei Scharlach, *Zentralbl. f. inn. Med.* **60**: 577, 593, 1939.

5. Thenebe, C. L., Cenci, V. P., and Hirschberg, M. S.: Scarlet Fever, *Arch. Pediat.* **51**: 615 (Oct.) 1934. Arnott, W. M.; Kellar, R. J., and Matthew, G. D.: Experimental Glomerulonephritis Produced by Use of Specific Sera, *Edinburgh M. J.* **43**: 233 (April) 1936. Duval, C. W., and Hibbard, R. J.: Scarlatinal Nephritis Experimentally Induced in the Dog, *Proc. Soc. Exper. Biol. & Med.* **24**: 876, 1927. Longcope.<sup>2</sup> Peters.<sup>20</sup> Friedemann and Deicher.<sup>11</sup> Escherich and Schick.<sup>17</sup> Pospischill and Weiss.<sup>18</sup> Box.<sup>19</sup> Schwenker and Comploier.<sup>9</sup>

6. Lyttle, J. D.: Addis Sediment Count in Scarlet Fever, *J. Clin. Investigation* **12**: 95 (Jan.) 1933.

of persistent hemorrhagic glomerulonephritis after scarlet fever in which the extraction of obviously diseased tonsils was followed by prompt clearing of the symptoms of nephritis. He warns against this operation in the acute stage. Others,<sup>22</sup> including myself, have seen recovery follow tonsillectomy after the acute stage of the nephritis has subsided, but this result is not always to be expected. Indeed, one should not be too ready to incriminate the tonsils, as is brought out by the recent study of Illingsworth<sup>23</sup> on the relation of tonsillectomy to nephritis in childhood.

I have investigated the incidence of nephritis in patients with and without tonsils at the Haynes Memorial Hospital. Over the period of time covered by 1,000 patients who were admitted for scarlet fever with their tonsils intact, there were 200 instances of scarlet fever in patients whose tonsils had been extracted prior to admission. The cases in the two groups were equalized as to age groups and seasons of the year, and no cases were included which showed complications on admission. The incidence of acute nephritis was 1.7 in those who had their tonsils in and 1.5 in those whose tonsils had been previously removed. Thus the difference was insignificant. In all fairness it is pertinent to remark that the tonsillectomized patients presumably had had defective tonsils and that they might not have fared so well had their tonsils been in during the scarlet fever.

The literature on scarlet fever fairly teems with conflicting notions regarding dietary causes of nephritis. Because albumin was found in the urine in nephritis, scarlet fever patients were forbidden eggs and meat; in fact, some were kept largely on milk. Thirty years ago it was shown that a prolonged milk diet was entirely ineffective in preventing nephritis and that patients actually fared better in general on a mixed diet containing eggs and meat during the postfebrile stage.<sup>24</sup> This has been subsequently confirmed.<sup>24</sup> These results were immediately explained on the ground of the protein content in the milk. As warnings against protein were dispelled, the dangers of fats were brought to the fore. The milk fat was then incriminated as an explanation of the poor results of the milk diet. A warning was given even against cod liver oil because of the fat. Next came a warning against potatoes because of the potash content—another example of dietary deprivation on unwarranted speculation, a common form of therapeutic tyranny. Today most scarlet fever patients enjoy a liberal diet consistent with their age. Salt, eggs and meat in reasonable quantities are now permitted during convalescence. In fact, diet as a cause of scarlet fever nephritis is an obsolete theory, except that an impoverished diet predisposes to all the complications of this disease, including nephritis.

Eight years ago Osman's method of administering alkali with the idea of preventing nephritis was used by Peters<sup>25</sup> with apparent success in a series of cases in England, but in 1937 the same author, in conjunction with Cullum,<sup>26</sup> proved its inefficacy during an epidemic

in which nephritis was prevalent. The incidence of nephritis in cases treated with Osman's method was 4.3 per cent and in the controls 4.1 per cent.

The fact must not be lost sight of that true nephritis is actually an infrequent complication of scarlet fever. The incidence reported from hospitals is, of course, higher than in the general run, since many cases are referred to the hospital because of the nephritis.<sup>27</sup> If we exclude all those cases admitted because of nephritis, we find an average of about 1 per cent, with wide variations in different epidemics ranging as high as 7 per cent.<sup>28</sup> In fact, in one epidemic in Poland an incidence of 19 per cent was reported.<sup>17</sup>

The symptoms, prognosis and treatment do not differ from glomerulonephritis of non-scarlet fever origin: vomiting, fever, polymorphonuclear leukocytosis, albuminuria, granular and hyaline casts, merging into hematuria, with edema first appearing in the face, often but not always hypertension, an increase in the nonprotein

*Nephritis in Nontonsillectomized and Tonsillectomized  
Patients with Scarlet Fever*

Concurrent series of equal age groups over the same period at Haynes Memorial Hospital:

	Number of Cases	Nephritis, per Cent
Patients with tonsils .....	1,000	1.7
Patients without tonsils .....	200	1.5

nitrogen content of the blood, anuria and finally uremia, which occurs in about 20 per cent of the nephritis cases. The prognosis is gaged by the severity of these signs and symptoms and their duration. If the condition clears promptly, the kidneys are not permanently affected. Prolonged albuminuria is a bad sign, but this must always be differentiated from orthostatic albuminuria. While cases of protracted glomerulonephritis do go on to complete recovery, there are some that go over into the progressive type.

In the treatment, one must keep in mind not only the condition in the kidneys but the conditions set up elsewhere in the body. The kidneys need rest, but this can be carried to extremes in the curtailment both of fluids and of nutrition. Dehydration is to be avoided, and 5 or 10 per cent dextrose intravenously may be indicated in spite of edema if the patient refuses liquids or is vomiting. In fact, intravenous dextrose solution is the best means of promoting diuresis. Diuretic drugs are best avoided. In my experience the condition of uremia itself is not benefited by bleeding. Even with an alarmingly high concentration of nonprotein nitrogen, creatinine and urea in the blood, the glomeruli may regain their normal function under conservative care.<sup>29</sup>

27. In 10,000 cases of scarlet fever treated at the Haynes Memorial Hospital there were 232 cases of nephritis (2.32 per cent). One half (112) of these cases were admitted during convalescence because of severe nephritis. Neu<sup>4</sup> had forty-four cases of glomerulonephritis in 1,845 cases of scarlet fever. Among these forty-four there were eleven admitted because of the nephritis. In addition there were five cases of "acute interstitial nephritis" due to bacteremia, all of which had a fatal termination, the diagnosis being established by autopsy.

28. Hunt, L. W.: The Treatment of Scarlet Fever with Antitoxin, *J. A. M. A.* 101:1444 (Nov. 4) 1933. Place, E. H.: Treatment of Scarlet Fever, *New England J. Med.* 205:225 (July 30) 1931. Joe, A., and Williamson, A. B.: A Note on a Severe Type of Scarlet Fever Nephritis, *Edinburgh M. J.* 33:49 (Feb.) 1926. Neu,<sup>4</sup> E-scherich and Schick.<sup>17</sup>

29. The recent studies of Smith and his associates (Chasis, Herbert, and Smith, Homer W.: The Excretion of Urea in Normal Man and in Subjects with Glomerulonephritis, *J. Clin. Investigation* 17:347 [May] 1938. Chasis, Herbert; Ranges, Hilbert A.; Goldring, William, and Smith, Homer W.: The Control of Renal Blood Flow and Glomerular Filtration in Normal Man, *ibid.* 17:683 [Sept.] 1938. Smith, Homer W.: New Aspects of Renal Physiology, *J. Urol.* 41:867 [June] 1939) show that the elevation of blood urea in glomerulonephritis results from decreased filtration along with decreased reabsorption. "As the capacity to reabsorb water is impaired by disease, the fraction of urea reabsorbed decreases, so that the urea clearance approaches the rate of glomerular filtration" (Chasis and Smith).

22. Underwood, E. A.: Early Nephritis in Scarlatina, *Brit. J. Child. Dis.* 28:114 (April-June) 1931. Hunt, G. P.: A Survey of Tonsillectomy and Adenoidectomy in Scarlet Fever, *New England J. Med.* 212:665 (April 11) 1935. Alport, A. C.: Focal Sepsis as a Cause of Nephritis, *Lancet* 1:1247 (June 11) 1932.

23. Illingsworth, R. S.: Tonsillectomy and Nephritis of Childhood, *Lancet* 2:1013 (Nov. 11) 1939.

24. Jochmann, Georg: *Lehrbuch der Infektionskrankheiten*, Berlin, Julius Springer, 1924, p. 728. Gestley, J. R.: Der Beziehung der Diät zu Verlauf, Blutbefund und Nephritis beim Scharlach, *Monatsschr. f. Kinderh.* 12:121, 1913.

25. Peters, B. A.: The Prevention of Renal Complications Following Scarlet Fever, *Practitioner* 129:614 (Nov.) 1932.

26. Peters, B. A., and Cullum, I. M.: Postscarlatinal Nephritis: A Study in Prevention, *Brit. M. J.* 1:1020 (May 15) 1937.

Blackfan and McKhann<sup>30</sup> have pointed out a condition which is often confused with uremia but which is unrelated to the retention of nitrogenous end products. I refer to the cerebral edema which may result from acute glomerulonephritis. Cerebral edema brings about a rapid rise in the blood pressure with severe headache, blurring of vision, vomiting, often a slowing of the heart and respiration, convulsions and coma. Magnesium sulfate by mouth in doses of from 1 to 2 ounces (30 to 60 cc.) of a 50 per cent solution has proved of value in relieving these cerebral symptoms. In emergency it may be given intramuscularly, 0.2 cc. of a 25 per cent solution per kilogram of body weight, repeated every four to six hours, as the symptoms require,<sup>31</sup> in conjunction with the oral administration of the salt.

In the absence of cerebral edema the possible disadvantages of magnesium sulfate and other saline laxatives need due consideration. Cardiac decompensation may become an important factor, and this condition calls for digitalis. It is well to keep the patient warm, but it is neither necessary nor advisable to try to keep him bathed in sweat. Fruit juices at first, followed later by the addition of milk and cereals, form the accepted diet. As improvement takes place, the diet is gradually increased in quantity and variety to that consistent with the normal needs of the age of the patient. Hypotheses running counter to established clinical experience should never be allowed to supersede the physiologic and pathologic problems presented by the individual case.

## THE CHILD-PARENT RELATIONSHIP

THE CHILD IN THE FAMILY

CLIFFORD SWEET, M.D.

LAWRENCE R. JACOBUS, M.D.

AND

HENRY E. STAFFORD, M.D.

OAKLAND, CALIF.

During the earlier years of the practice of pediatrics as a specialty it was entirely natural for the main emphasis to fall on the physical care of the child, since with few exceptions only sick children were brought to the pediatrician. Then too, in that not so distant day, parents had fewer problems than they face today. As yet no doubt had arisen in their minds concerning their absolute authority over their children. While "Spare the rod and spoil the child" has been found to have limitations, it has the great virtue of simplicity and produced results in many generations of men that may well cause us to give some earnest thought to the values of parental authority as a sound teaching method even though we have found better means for its exhibition. It is said the Dutch early discovered that a blow on the bottom of a child let knowledge in at the top. This is not a plea for the return of frequent corporal punishment, but we want to bring out clearly the absolute necessity for the exercise of reasonable authority by the adult in any relationship he may have with a child for whom he cares. All lives must be divided between the

things we like to do and those we must do. We would like to give every one as many as possible of the things one likes to do, but if we give one too many of these and one neglects the things one should do too much one cannot become a useful, emotionally stable, self-disciplined and, therefore, a happy human being.

Young, inexperienced parents who are taught to understand the ways of children and are thereby able to manage them skilfully with a minimum of friction and worry grow naturally in the direction of grace and wisdom. On the other hand, the worry that always accompanies lack of knowledge and skill accentuates their own faults of character and lack of emotional development and any incompatibilities that happen to mar their married relationship. For example, if either is a selfish person his self-centered attitude becomes more pronounced as he defends himself against the unnecessary fear, fatigue and feeling of futility which his blundering, uninstructed attempts at carrying out his parental duties bring in their train. However, when he is helped sufficiently, especially while he is in the happy glow of pride that accompanies the birth of his child, to be reasonably successful, he is caught up and carried along by the tide of his success into a happy state of mind that even enables him to brag most inordinately about his "good child" and by inference his own virtues when he talks with his less fortunate peers.

The physician who talks with parents when their children are young has the best opportunity to help them establish a satisfactory family life. Parents' attitudes are not formed or have not yet become so fixed that they cannot be improved. We therefore present in this paper some of the methods by which we attempt to instruct and help the parents who consult us concerning their children.

Nearly all these children are brought to us because some concern for their physical well-being has arisen in the minds of their parents. However, the physical welfare of the child, primary and fundamental though it must always remain, must be only one of the chief concerns of those who guide the lives of children.<sup>1</sup> In order to emphasize this thought to parents we often say "It is far better to be a reasonable, lovable human being who can live happily with his fellows, even though his health isn't altogether perfect, than to be the healthiest 'animal' in creation."

### FATHER'S PLACE IN THE FAMILY

From the beginning the parents must clearly understand that the admission of a new member to the circle demands readjustment of all the existing relationships between or among those who constitute the family. True enough, the family forms a natural group, and since at first the newcomer, being an infant, demands but little, the adjustments are simple and, if understood, are easily made. However, since they are beginnings, they are singularly important. A complete family life demands an actively participating father. Financial responsibility is not enough. He must grow in that wisdom which alone makes possible an understanding of the nature of a growing child and which can be learned only by those who share deeply and constantly in the care and upbringing of children. At the beginning, while the young father's pride is at the full, is the time to draw him into the newly expanded family life rather than to exclude him with that all too often used caustic remark "Get on out of here, you don't

30. Blackfan, K. D., and McKhann, C. F.: Acute Glomerular Nephritis in Children: Treatment of Cerebral Manifestations, J. A. M. A. 97: 1052 (Oct. 10) 1931.

31. Ellis, L. B.: The Treatment of Bright's Disease and Related Renal Infections, New England J. Med. 216: 821 (May 13) 1937. Blackfan and McKhann.<sup>30</sup>

Read before the Section on Pediatrics at the Ninety-First Annual Session of the American Medical Association, New York, June 12, 1940.

1. Sweet, Clifford: Opportunities in Pediatric Practice, J. A. M. A. 111: 893 (Sept. 3) 1938.

know anything about a baby," merely because he expresses some of the foolish ideas about children which seem to be an inescapable, though fortunately a temporary, part of that gigantic expansion of the ego which comes to every man each time he becomes a full-fledged member of the ancient and honorable order of fathers. We know of no greater service any pediatrician can do than to start two young, inexperienced parents working together more closely and harmoniously than they might otherwise do. We therefore make opportunities to talk with the father and encourage him to consult us for an explanation of any of our rules or ideas of which the underlying reason is not readily apparent to him and offer ourselves as arbiters in all differences of opinion that arise between parents and even those that emanate from the grandparents.

#### MATERNAL FEAR

Every mother must be encouraged after the birth of her first infant to control her fears that her infant may be too fragile to live. This must be done by truthfully reporting to her or letting her observe careful, complete physical examination of her infant as the basis for assurance that her baby is entirely normal. Her fears cannot be allayed if she has even a suspicion that her child's physician has taken her infant with too casual an attitude. Next her fears must be discussed in perfect frankness and friendliness so that she admits them freely and without shame. This she can easily do, once we have convinced her that such fears are in no way peculiar to her but have been in similar measure the lot of every woman who has known the joy of motherhood. Once any fear ceases to be regarded as an evidence of one's own weakness and, therefore, shameful and is recognized as a universal reaction of all mankind to similar circumstances, it loses its importance to a remarkable degree.

#### CRYING

Every child cries more or less and some cry more than others, just as some fathers swear more than others. If parents understand this and therefore seek by intelligent investigation to diminish crying to its lowest reasonable level, the beginnings of sound psychologic adjustments are firmly laid. On the other hand, if the parents are not taught by long and careful effort to understand the true meaning of their infants' crying, their state of mind is clearly revealed by "My baby cries because he is bad," and the beginnings for an unpleasant and unfortunate relationship are formed. Crying is for some time after birth the baby's only means of attracting attention to his needs and desires. Therefore, until he acquires other means of announcing his needs or demanding his fair share of the attention and his other rights as a member of the family, he must perforce rely entirely on his ability to cry, a clear demonstration, we submit, of a highly intelligent use of very limited resources rather than of original or any other kind of sin. Crying, like all other disagreeable behavior, is used by an intelligent child as his chief method of gaining his desires and needs after more grown-up methods, such as speech, should be substituted for it, only as it continues to be his most effective method.

#### INDIGESTION ("COLIC")

Any baby may be made uncomfortable by his digestive tract. While we have no accurate method of measuring the amount of his discomfort, we use this term rather than pain advisedly. In all probability it is only those children who have actual spasm of the pylorus or other

regions in the digestive tube due to hypersensitivity to some of their food intake who suffer discomfort which is of a degree that reaches actual pain.<sup>2</sup> Every reasonable effort must be made to relieve his discomfort, but beyond this he must bear the irreducible minimum with fortitude as part of the common human lot in which no one can be constantly comfortable or always happy. Even at his tender age he must begin to learn that he cannot inflict those about him with his most disagreeable behavior whenever he is uncomfortable. Then too we must emphasize that the discomfort of indigestion or that which comes from overeating is not relieved by being constantly carried about. Also, since we have no way of measuring the discomfort of another, it is absolutely necessary to find out by observation how much of the baby's outcry is due to discomfort and how much of it is his natural desire for attention at the time of his choosing. Since crying is entirely harmless to any infant, he must be allowed to cry it out. Only in this way can the approximate level of his discomfort be distinguished from his demands for attention and from the irritability of his immature and easily fatigued nervous system which is produced by too much handling, too prolonged overstimulation from association with older members of the family and too little rest.

#### REGULARITY

There can be no doubt that a regular schedule is the most efficient and least wearing way of performing a regularly recurring task. Consequently, parents should be encouraged to follow a regular schedule, although regularity must be so tempered with reason that it serves them rather than that they become the servants of regularity. However, the greatest effect of regularity is the peace that it brings to the parents' minds and the discipline which it begins in the mind and character of the child. When any one discovers that all one's wishes are not the law of the family, one begins to realize for the first time that the wishes of others must be taken into consideration. Fortunately also one soon becomes accustomed to the schedule and is far happier than one would otherwise be.

#### CHANGE OF PROGRAM

Any departure from a regular program, if displeasing to the child, will be resisted vigorously, while if it is pleasing he will seize on it and attempt with all his powers to make it permanent. Daily we hear from parents "Doctor, he was all right until I attempted to give him coarser food or until I put him into a new bed or until, after letting him sit up late during that hot spell, I went back to his old time as the weather cooled or until he awakened in the night and I took him into my bed or until we visited his grandparents or until he wouldn't eat and I coaxed him, and, Doctor, I've had to coax him or amuse him ever since<sup>3</sup> or, most frequently, until he became ill (perhaps with a minor illness), since which time he demands all the immunities and privileges of a permanent invalid or else he won't follow any of my wishes."<sup>4</sup> So it goes, until, until, until, until it has become apparent to us that a graphic picture of any human life can be drawn with two intersecting lines to represent roads or ways of life with the town of "Until" marking the crossroads. The human

2. Stafford, Henry E.: Abdominal Allergy in Children, *California & West. Med.* **34**: 168-172 (March) 1931.

3. Sweet, Clifford: My Child Won't Eat, *Arch. Pediat.* **47**: 582-588 (Sept.) 1930; Voluntary Food Habits of Normal Children, *J. A. M. A.* **107**: 765-767 (Sept. 5) 1936.

4. Sweet, Clifford: Infection and Behavior, *Arch. Pediat.* **49**: 190-194 (March) 1932.



being going along the main well traveled familiar way of early life arrives at "Until," when he must turn aside to a more grown-up and therefore less familiar and more arduous route, into which he must be led and helped over with affection, understanding, skill and persistence. Or some circumstance, for example illness, brings him to an "until" which has no permanent place on the map of life, a mere tent city, to which, after a side excursion, he must return and again follow the main highway. He may find the excursion pleasant and have a strong desire to retain permanently all the perquisites which were temporarily entirely within his rights. If this is so he must be taken by the hand with the same love, understanding and, above all, persistence and his feet again set firmly on the main road.

#### DIFFICULT BEGINNINGS

So one may think of all education as a departure from an old road, a change of route. Any individual may find great, even seemingly unsurmountable, difficulties at a beginning which for others may be too easy to attract more than passing attention. If, in the face of his difficulty, he is too suddenly forced, shamed or given an opportunity to use his apparent inability as a means of gaining pity, sympathy, attention or some other desired advantage or, even as Job of old, to gain distinction by cursing the day of his birth, long lived or permanent disability may result. This long life or permanence rests on the real difficulty plus the belief that the difficulty is unsurmountable, and often on its value as an excuse to follow the easier path, thus avoiding other related or unrelated difficulties that arise later. On the other hand, if the beginning is made so easy that at least reasonably good results can be accomplished and, as skill is increased, gradually increasing effort is demanded, soon the desired goal or at least a satisfactory level of accomplishment is reached without conflict and with an increased self confidence which is altogether the best equipment for further advance toward successful living. As a single example let us consider the necessary change from liquid to solid food. Most children welcome the change if it is not too abrupt, others can easily swallow very coarse particles with surprising ease, while still others are literally choked by the uncontrollable (probably reflex) reaction set up in their throats by the very texture of the newly offered food. Members of this last group are often brought to us as late as 5 or 6 years of age as "bad children, who will not eat any solid food." When any child has difficulty, he should be met on the ground of his own choosing, not for battle but for training. The new food having been made as fine and as smooth as he wishes, should very gradually be changed to the texture and consistency desirable for his age, having in mind that individual tastes often vary throughout life in the size of the food particles one swallows, and Alvarez<sup>5</sup> has recently denied the increased nutritive value of "fletcherized" food whether the process of trituration is carried on before or during eating.

#### BASIS OF PARENTAL AUTHORITY

That parents should constantly exercise authority over their children becomes axiomatic when one gives it thought. The parents have all responsibility and the children none. Responsibility without the support of adequate powers cannot be borne long by any one without inevitable failure to endure its weight or to

make constructive use of it. The choice of a leader is soundly based, in large measure, on his experience in the field into which advance is proposed. Since life remains entirely unexplored and unknown to the child, he needs the guidance of the more experienced adult. Intelligence develops with years of growth and certainly is a large and necessary part of the qualifications for leadership and authority. Every child begins life completely self centered, and only by long training and by the fundamental necessity of living successfully with other human beings does he begin to give thought to the wishes, rights and well-being of others. Every normal adult has advanced at least some way along the way of living with and influencing his fellow creatures, and, when he becomes a parent, usually his parental affection for his child carries him a long way toward generosity and consideration for his child.

We are moved within our own natures and lead others only as we develop our reason and learn to use fully but control wisely our emotions. Reason is a faculty which matures slowly only in the soil of a developing intelligence and increasing experience. Control of the emotions, a gradual tempering process in reason, experience and increasing intelligence is a function of growing up. In fact, the child possessed at birth of all the emotions must learn their use and control throughout his entire life time and the level of his attainment is the true measure of his adult stature, no matter how great his physical bulk and intellectual development may become.

There remains another reason, perhaps more important than any one of the others, for parental control of the child. All parents, unless they are indeed depraved individuals, love their child far more than the child loves them. The very young child clings to his adult attendants and feels his greatest security in their familiar presence, but in all probability beyond the satisfaction of his needs and the calming of his fears he gains emotional attachment to any individual slowly. This can hardly be doubted by any one who has seen a child transfer his allegiance after a few days to any one who is kind to him, and if his parent or usual attendant is absent for even a short time he is readily forgotten and is not restored to full favor at once. If parents are not warned that this lack of deep emotional attachment is in every child, they may think somehow they have failed to win the child's love and will consequently fail to discipline him wisely and when the child is old enough to say "Well, then I won't love you any more," the poor parent is thrown into a state of subjection which is detrimental to the whole child-parent relationship.

#### USE OF PARENTAL AUTHORITY

While parental authority is soundly based on the greater development of the adult, it must be used on reasonable, clearly defined principles if it is to produce such desirable results as the safety, discipline and best possible development of the child and at the same time win his respect, admiration, gratitude and lasting love for the parent. A decision which is made for adequate and valid reasons can be carried out against prolonged opposition and even violent emotional storms. On the other hand, a decision made with equal firmness and authority which arises without due thought or for the enforcement of which there is no real reason is abandoned so readily in the face of opposition that the parent may justly be thought inconsistent and the child is encouraged by victory to oppose all decisions that are

5. Alvarez, W. C.: *An Introduction to Gastro-Enterology*, New York, Paul B. Hoeber, Inc., 1939, p. 259.

distasteful to him by any and all means that he may find useful. At the same time the poor child fails to find the support he should gain from a familiar and reasonable discipline. So, confusion is added to confusion as he attempts to make his way along an as yet unfamiliar path in the company of parents whose behavior in two sets of identical or largely similar circumstances he cannot possibly predict.

A child should be free to follow his own desires except when some reason forbids that he should do so. For example, he may wish to play with a beautiful dish which is unbreakable but contains a deadly poison. His parent will not let him have it and will persist in his refusal to the point of physical restraint, unmoved by any kind of show the child may put on. However, when the dish is empty and there is no reason for the child not having it, all too often the parent says "No!" as promptly and sternly as he did when it contained poison. Then, when whining and crying, begging or a tantrum has annoyed him sufficiently, he says, with great irritation, "Oh! go ahead and take it, you bad child." Can any one honestly blame the child for trying every decision of his parents to see whether or not it will hold when he can so easily reverse many of them? Also can any one be even mildly surprised if the child who finds disagreeable behavior his most effective weapon continues using it so frequently in his after life that he brings much unhappiness on himself and others? Cannot any one understand the exaggerated importance of attaining the object of his desire when he has been aroused to a high emotional pitch by unnecessary opposition and the lasting impression produced by a final victory when it is his? Until they are taught or learn otherwise, nearly all parents answer "No!" too often and too readily in response to too great a number of the child's requests.

#### THE "NO" PARENT

There are many reasons for this too ready negative response to the child's wishes. The first arises from another of the fundamental differences between an adult and a child, a difference which is often annoying to the adult and which will wear his patience to the breaking point unless he fully understands that his child is behaving in a perfectly normal manner. The child is incapable of prolonged attention to or concentration on any single matter. Also, having no duties or responsibilities, his attention is held only as long as his naturally short-lived interest is stimulated. Consequently the adult with his greater powers of concentration and his need for completing necessary and many times unpleasant tasks is all too frequently annoyed and pestered by the child's incessant demands for attention and change of activity until his temper is short indeed. If the child is old enough to pull out drawers, turn on the gas, get into the toilet, break dishes or bric-a-brac or injure himself by burns, falls or in some other manner, the enormous strain on the nervous system of the mother while she attempts to work and at the same time keep her child out of mischief is more than any one can or should be subjected to. No wonder she is soon irritated beyond all reason as she jerks her child away from one thing after another and finally slaps his hands, to the accompaniment of the thought that she has a bad child and certainly is a failure as a mother. All because no one has explained to her that her child is a normal human being for his years, who, if he weren't active and eternally curious, could never be educated and that she

cannot teach him "to let things alone" by commands and force. We often ask a distracted mother how well she thinks our secretaries and nurses could do their tasks if each at the same time had charge of an active child who had the run of the entire office.

The second in importance is that any adult needs refreshment, which comes only with release from being constantly in charge of a child. Every mother should have some regular time away from her child, and the father and mother should have as many times as possible during which they can return for a few hours at least to the direct dual relationship of their courtship and early marriage days with no one, not even their dearly beloved child, "between" them. Children who are put to bed regularly at an early hour are doubly fortunate. They get much needed physical rest and, more important, they have parents who, rested from their cares, are more reasonable and patient than they otherwise would be. Mothers must be encouraged to get away from their children with the assurance that they will be better mothers when they return and that the best mother must at the same time be the best wife. If the family budget or sensible available as well as obliging relatives do not allow the mother a reasonable amount of freedom, she can surely find another young woman in a like predicament who will care for the children of both in return for a like service at another time.

#### METHOD OF CARE FOR RUNABOUT CHILD

When the mother has tasks to perform, her child should be put in a safe place, perhaps a pen or a room with a gate across the door where he can see and be seen by his mother. Then while she does her work quickly and effectively her child begins to learn to rely more and more on himself. As the child learns to rely on himself, his periods of concentration grow in length and, more important still, he learns another part of that most valuable lesson which teaches him that he must shape his life according to the wishes of others as well as his own. He will soon learn to play contentedly by himself for reasonably long periods of time if his cries of protest are disregarded when he is first put into his pen or other place of safety and if they receive the same disregard when he renews them with all his might after some break in his routine, such as illness, a visit away from home, or after a visit from Grandmother, who just couldn't let "the poor little dear stay in that horrid old pen," or after father's day at home when he was taken for a walk at the usual hour of his lesson in self reliance.

The child can see no reason why he should not turn on the faucets and wet his clothing several times daily. Certainly to him turning on faucets cannot be other than a natural and usual act, since he sees both his parents do it many times each day. Also dabbling in water and starting it flowing as the result of his own discovery that he can do it are great pleasures. Therefore, when his mother is busy with other things he should be effectively kept away from the faucets, or when he has the run of the house, the water should be turned off below the basins that he can reach. It is also easy to keep him out of the bath room by placing a hook or other simple door fastener on the door above his reach. He should not, however, be denied the pleasure of turning on faucets and holding his hands in running water. A box of suitable height placed before the basin for the child to stand on while his



parent stands behind him with arms encircling him for safety from falling while he can plunge his hands into the water and experience the great delight of rubbing them together while they are covered with soap make getting washed a pleasure to all concerned. Contrast this with the scene made up of the irritable parent and the unwilling child being dabbed with a wash cloth while he struggles whenever he has a free hand to grab the forbidden faucet or the cake of soap, and the advantage of the first method will need no further exposition. If faucets and running water still give the child great pleasure, some of the voluntary attention to which every child is entitled may be profitably spent gratifying his desire.

#### METHOD OF DISCIPLINE

When the runabout child gets into mischief, such as climbing up to the sink filled with the breakfast dishes, he should not be scolded or slapped but should be removed to his usual safe depository as a matter of course without comment. Such an action, when done without an accompaniment of verbal threats and lamentations that a so virtuous parent can have a so depraved child, has an air of finality and accomplishes its sole purpose, namely the removal of the child to his own limited sphere of activity until his mother has time to give him attention.

Since throughout life, and especially during childhood, association of events with places is strong, it is unwise to punish a child by putting him into the place, such as his pen or his bed, where he is expected to spend much time alone in a reasonably happy state of mind. During early childhood only a few associations are present in the child's mind, but these few are strong, simple and direct. The place in which he is regularly given food soon becomes strongly associated with eating and he may be greatly disturbed by any change in its location or equipment. Nearly all children associate even their table implements with certain kinds of food and resist any attempt to change the usual procedure. Any child who is given his milk from a bottle until after he is old enough to take it from a cup clings to the bottle not only because of his long and pleasant association with it ("Oh! but Doctor, he just loves his bottle so") but also because he regards taking milk in any other manner as peculiar, and who can say that he is not already beginning to defend his desires on the grounds of righteousness and morals. If he could express his thoughts he might well say "'Tain't right and decent to take milk from a cup. I've never heard of such a thing and what will people say if I do it?"

#### WHAT IS A "SPOILED CHILD"

Some one may think when one reads that a child should be taught to fend for himself that our idea is that he should be treated more or less mechanically. On the contrary, we want every child to have plenty of attention and affection. However, both attention and affection must come to him spontaneously out of his parent's love and wisdom rather than be thrown to him as an appeasement lest he make himself too disagreeable for toleration. Time and thought must be allotted for his training and his pleasure. But when the necessities of life demand that his time must be changed or temporarily curtailed, his lack of understanding or his displeasure must not become the scourge which drives his unwilling parents to give him grudgingly the attention which he demands and needs with disagreeable methods coming to have too great a value

in his mind. A spoiled individual of any age is one who too frequently or too exclusively uses disagreeable methods to get whatever it is he may want.

#### PARENT AND CHILD

Any relationship between human beings that gives lasting satisfaction and grows toward its greatest possible nobility and beauty must rest on mutual helpfulness. Each must give to the other, at the cost of some sacrifice, that which he possesses and the other needs. No one can for long continue making gifts that come from the heart unless one receives in return some recompense, some satisfaction of one's own needs that replenishes the well springs of one's affection and generosity. This return need not be material; indeed, if it is too largely so it will fall short of its greatest value, the enrichment of the giver. On the other hand, the one who takes all the gifts and makes no adequate return suffers an inevitable impoverishment of the spirit which leads to poverty indeed.

Consequently, if the child develops as he should while under the influence of his parents, he must be taught to give as much as possible to his parents in return for their care for him. If no demands are made on him, he gives rise to that question so frequently asked "Why do the most unselfish parents have such selfish children?" At the beginning of his life in the family the child makes sufficient contribution by the joy of his presence. However, this joy is soon diminished if he is not taught to make only reasonable demands for attention. This first contribution is to take over more and more of his own care, at least to the extent of amusing himself for greater and greater parts of the day. Still later he must be encouraged to wait on himself whenever that is possible and to assist his parents by doing any errand within the household that he is capable of doing. Then certain duties, for example drying the dishes and setting the table for meals or cutting the lawn should be his, even though his parent could do them more easily himself, and any complaint he may make only indicates that he has a fair and normal share of that laziness which is a characteristic of all mankind. Parental authority should have such weight that he fully realizes that there is no way of escaping his assigned duties, but the austerity of sheer authority and the drudgery of labor can and should be greatly softened by the pleasure which comes to each member of a team with accomplishment and the fair distribution of praise. Also when all are free after tasks are done there should be a time set aside when all, young and old, play together. Reading aloud or telling stories in which all children delight, playing simple games such as marbles or tiddlywink, taking needed exercises for improvement of the mechanics of the body which are relieved of all tedium and made gay with laughter, especially when Daddy and Mother take an active and undignified part, singing together (never mind the lack of harmony or the neighbors), a quiet time for talk when the child can tell of all the interesting things of his day and have answers to his questions, and then at last to lead a gay procession up the stairs to bed on Daddy's back makes each day a part of the richness of life, living in pleasant memories and making beauty and balance the very warp and woof of the young lives as they grow and expand toward the fulness of their powers, not to mention giving the parents the greatest happiness that comes in this old world.

## ABSTRACT OF DISCUSSION

DR. OSCAR REISS, Los Angeles: At a time like this it seems most fitting that a paper such as this should be presented before this section. The pediatrician can play an important role by teaching parents a way of life for their children that helps to establish stable emotional patterns and clean minds as well as sturdy bodies. More important than ever does the teaching of mental hygiene by the pediatrician loom up as one of the vital tasks for him to undertake. To do this effectively calls for a careful study of the total environment into which each newborn infant inescapably enters. He must know not only about the parents but also about all the other members of the household, as well as the character of the physical surroundings and the economic status. I hope the time is fast disappearing when the children's specialist devotes all his time during the periodic visits of the young infant to his office to an exploration into the various orifices of the body and other gestures of an examination, often unnecessary to an understanding of the nutritional state, for these visits offer a great opportunity of educating mothers, of imparting to them authentic information concerning the best care of their young, and of debunking much of the misinformation supplied over the radio and by kindly but ignorant friends and neighbors. It behooves us to rise to the broader task before us, to prove authoritative in every phase of child care, to play our part in the development of a new generation of young people fit for the democratic way of life.

DR. EDWARD LISS, New York: One gets enlightenment listening to a paper so packed with wisdom, perhaps because the authors come from Oakland, an area in which I presume the population is more sensitive to current mental hygiene practices, probably, than any other part of the country. The authors reflect the education which so many of our colleges, as pioneers, have already accomplished. As one evaluates the percentage of failure in the somatic areas, one wonders if the entire problem in review is whether allergic problems are not so much alone a question of somatic insufficiency or whether they are something beyond just the somatic area. Most discussions are confined either to the somatic or to the psychologic area. Rarely is an attempt made to integrate this needful and very purposeful interrelationship. Parent-child relationships distinctly affect the prognosis of every somatic problem, for how can any individual be the object of so much well intentioned attention and yet feel that certain aspects of his growth are not particularly significant? I think that any chronic somatic problem brings with it definite emotional repercussions, which are as needful of attention as anything that takes place in the laboratory or in the office. One of the perils which the pediatrician has to overcome in this area is that reeducation of the parents is an extremely slow procedure. It is accompanied by a great deal of resistance, and this resistance must be appreciated as being natural and not of necessity stupidity. Human beings build up patterns for living. If these patterns turn out to be unsuccessful, they must be carefully removed only through some adequate substitution, and substitution is a slow procedure. I hope that the Section on Pediatrics will concern itself with the psychic aspects of disease as much as it has with the somatic. If it does, pediatrics is facing an era of function which is beyond anything it has faced up to the present time.

DR. CLIFFORD D. SWEET, Oakland, Calif.: I hope Dr. Liss did not mean that I merely reflect the interest in child welfare in my community, because I have had something to do over the past twenty years in forming it. It is a necessary ideal for any man, particularly a pediatrician, that he attempt to make the community in which he lives a better place for children. We have an active and interested school department in Oakland, with a full time pediatrician in charge of the school health. We have more and better children's dentistry than any other place in the world. One cannot live in such an atmosphere without being affected by it; but one cannot float, one has to work. I agree with Dr. Reiss that one must not lose one's opportunities because Johnny comes in with an earache, to find out how Johnny is living with his parents. It is interesting; it is not always materially rewarding, but it is

always tremendously rewarding in results, and one never knows when one starts a child in a given direction how far that child may go. A little girl was tearing up a magazine in my office. I said to her "My child, why do you tear that? You know books are our friends." She came back five years afterward, and her mother told me that from that day forward she had never mutilated a book of any kind and that she had frequently said to others "Don't tear that; books are our friends." If the pediatrician is really going to influence the attitudes of the people in the family, he must deal with the child and his parents on a basis of frankness, of understanding, of neither belittling nor scolding any of them, and of kindly firmness rather than cajolery in the face of necessary and unavoidable discomfort. I look on these recent tongue blades with candy on them as just another means of making it difficult to teach parents how to help their children grow up, while their doctor uses infantile methods even though he talks big.

A TYPE OF CHRONIC PERITONITIS  
APPARENTLY DUE TO INTESTINAL INFECTIONANTHONY BASSLER, M.D., LL.D.  
NEW YORK

The peritoneum itself is very resistant to infection. In this it probably represents a bactericidal ability beyond any other tissue in the body. This bactericidal ability is especially marked with intestinal organisms, such as those of the coliform group. That the peritoneum is constantly assailed by bacteria is suggested by the work of Roberts, Johnson and Bruckner,<sup>1</sup> in which it was shown that in 80 per cent of the instances, and irrespective of intraperitoneal inflammatory reaction, positive cultures were obtained. These differed from the bacteriology of the air and were of intestinal micro-organisms. In noninflammatory conditions a staphylococcus was recovered in 11.2 per cent. Ordinarily these organisms are cared for by the peritoneum, the lymph and vascular systems and the blood. While the ability of the peritoneum to destroy organisms is high, it apparently is not complete in that in 6 per cent of healthy persons on one vein tap positive blood cultures of low grade intestinal organisms were obtained,<sup>2</sup> this observation having been confirmed.<sup>3</sup>

The chronic forms of peritonitis have been classified as chronic simple, primary and secondary malignant, tuberculous, pneumococcic and hydatid. To make a distinction between these and the form about to be described, a brief pathologic presentation of the different types may be offered. The agglutinating process, which terminates in the fine adhesions so often encountered in the abdomen, is undoubtedly a local process in most instances. These are apparently protective processes resulting in membrane-like attachments which separate often at the slightest touch. The adhesion formations due to chronic peritonitis are more generalized than local and a much more organized and a more difficult tissue to handle. In the tuberculous form these fibro-adhesions are marked, the coils of the intestine are mostly freely movable excepting where adhered in localized areas. In the miliary and localized tumor formations, the appearance is characteristic. The

1. Roberts, Kingsley; Johnson, William W., and Bruckner, Helen Sue: The Aseptic Peritoneal Cavity: A Misnomer, *Surg., Gynec. & Obst.* 57: 752-761 (Dec.) 1933.

2. Bassler, Anthony: Intestinal Toxemia, Biologically Considered, Philadelphia, F. A. Davis Company, 1930.

3. Cameron, G. C.; Rae, C. A., and Murphy, G. N.: *Canad. M. A. J.* 25: 131-134 (Aug.) 1931, who report 6 per cent of positives in healthy subjects on only beef heart infusion as the medium.

primary and secondary malignant forms are localized affairs of the peritoneum, the noninvolved parts appearing normal.

In pneumococcic peritonitis there is abundant purulent fluid exudate that is characteristic, this contrasting sharply with the tuberculous form. This is further made definite by the generalized redness of the peritoneum without localized variations and, despite the disposition of the pneumococcus to form fibrin, there is little tendency to adhesion formation. Also of assistance toward diagnosis is the large quantity of purulent material that continues to escape from drainage tubes for days. Diffuse spreading gonorrheal peritonitis beyond the pelvis is rare, although a fine fibril coblike mesh may be seen about the liver surface. Usually the process is about the fallopian tubes, always seems to remain local in the pelvis, and there is much doubt that the gonococcus can cause a generalized peritonitis, the same being true with the hydatid form. There are instances of large areas of adhesions of a viscus, mainly the colon, that are protective processes and are not those fundamentally of a general peritonitis. The acute form of peritonitis is not presented, the type described being distinctly a chronic or continued process.

The peritonitis to be described is a very generalized disorder involving almost all of the peritoneal covering of the different organs in the abdomen. There are no distinct adhesions or localized adherent masses, and larger areas of the peritoneum are massed as if cemented together and separation of one organ from another without tearing into the intestine is quite impossible because of the fixity of the adherent areas and a friability of the tissues. Separation of one organ from another is impossible. The suggestion is that by way of some plastic material which covers large areas of peritoneum a generalized gluing together of structure takes place, the peritoneum being dull and thickened looking and of a yellowish pink. Instead of there being the fibrin type of adhesions more or less localized, or the glistening appearance, the peritoneum is thickened, dull and granular in appearance. Such free fluid as is present is very sparse and is viscid in character. On section of the peritoneum proper there is no area of a layer of sharply defined endothelial cells demonstrable. This is lost in a thickened viscid, edematous process with much cytologic evidence of a marked chronic inflammation which involves the peritoneum and the subperitoneal structures. The appearance of the abdomen mostly simulates that seen in chronic inflammation of the omentum but differs again in that there are no spheroidal nodules, fibrous formation or evidence of fat necrosis.

CASE 1.—The first instance of this disorder was observed in 1919 in a man of 47. There had been a long standing history of painful abdominal disturbance. The conditions mentioned were seen at operation. The patient died of a cerebral embolism on the eleventh day after operation. No special studies were made nor a postmortem examination performed.

CASE 2.—A woman aged 54, seen in 1926, had had an appendectomy thirty-one years before and a cholecystectomy twenty years before. Her illness particularly was of about two years' standing and the main symptoms were continued severe pain in the abdomen, indigestion and constipation. Her general health seemed good in that she looked well nourished. On examination her abdomen was generally tender to pressure, mostly in the umbilical region. The abdomen seemed stiffened to deep pressure, there being no rebound sign. The x-ray examination was not significant beyond there being definite stasis in the small and large intestine. The blood counts averaged 11,500 leukocytes and a polymorphonuclear count of about

82 per cent. The stool was markedly acid and high in anaerobes, with a predominance of *Staphylococcus albus*. At operation the abdominal appearances were as described. The small intestine was torn into twice in an attempt to identify the structure and to accomplish something operatively. Nothing more was done, the case proceeding with a fecal fistula of the small intestine, which she controlled with a colostomy bag. At the time of the operations, swabs were made of the peritoneum. The conditions found are presented after the next case. She lived twenty-nine months after the operation and was reported to have died of pneumonia, no postmortem examination having been made. What was interesting though was that the pain in her abdomen gradually subsided and about seven months after the operation was distinctly improved. This is of interest in connection with the following case in the improvement of the peritoneum noted between the two operations.

CASE 3.—An unmarried woman aged 54 was seen in 1939 whose main complaint was a "tightening" sensation in the chest and inability to breathe deeply on account of pain in the upper part of the abdomen, which she stated had been gradually getting worse for about ten years. She had had a hysterectomy at her thirty-sixth year because of menorrhagia from fibroids and in her forty-seventh year laparotomy in which an intestinal anastomosis with a button was done. The diagnosis then made was mass adhesions in the abdomen and intestinal obstruction. For two years before being seen by me she had been in poor health and unable to work, the main complaint being as mentioned. She seemed well nourished. Her abdomen was very tender and sensitive and seemed to be stiffened inside. No x-ray examination was made. The urine was high in phosphates, the  $p_n$  being 5.1, and otherwise normal. The stool was highly acid, soft and gassy. The bacteriology was high in *Staphylococcus albus*, *Streptococcus nonhaemolyticus*, *Clostridium putrificum* and the bacillus of malignant edema. She seemed to be slowly progressing with an intestinal obstruction and after about three weeks of observation was operated on. The interior of the abdomen presented the conditions mentioned in which the stomach and small and large intestine were massed together. In an attempt at separation, the intestine was torn in three places by only a gentle effort. From each of these openings there came a light yellow, gassy fluid. Swabs were taken of the peritoneum which showed mixed bacteria and on bacteriophage and lytic procedures gave a pure culture of *staphylococcus*. The operation was followed by a large fecal fistula through which foods taken by mouth came through in about five minutes, practically nothing passing by rectum up to the time she died, suggesting that the opening was high in the small intestine. While in the hospital for four months she slowly lost weight and continued to complain of abdominal pain in a gradually lessening way. In an attempt to reestablish a transit through the bowel and the hope of subsequently closing the fistulous tract, she was operated on again. At this time it was noted that a marked change had taken place in the appearance of the peritoneum. It now was much more normal looking. The adhesions present were those of the more common type, although separation of the organs was not any more possible because of their density. An entero-anastomosis was performed. She died ten days afterward, the postmortem examination revealing a suppurative peritonitis, necrosis of the bowel at the anastomosis, dense adhesions throughout the abdomen, and a granular degeneration of the liver and convoluted tubules of the kidneys. The bacteriology of the fluid in the abdomen was not determined because the infection was believed to be due to leaking from the necrosed intestine.

Since the swabs were the most interesting, only the bacteriologic studies of these in cases 2 and 3 will be presented in some detail because all the bacteria mentioned in these observations had at various times been recovered from the stools. In connection with the stools, however, it was notable that the organisms of the *B. coli* classification were almost absent at all times. The peritoneal swabs were grown aerobically and anaerobically in seventeen different mediums. Isolation attempts were engaged in through subculturing for identification.

In addition, the phagings of the mixed bacteria were studied by lytic tube procedures to note the most persistent of the organisms, this rather closely following the infectivity of most significance with intestinal bacteria. There was not much difference in both of these cases in the lytic studies. During the first four days in both cases the bacteria were mixed. Those identified in the anaerobic tubes were mostly *Alcaligenes bookeri*, *Clostridium saccharolyticum*, *welchii* and *filamentosum*, *Bacteroides dimorphus* and nonhemolytic streptococci. At the sixth and seventh days the anaerobic growths were negative, all the organisms having been phaged in the mediums. Some exceptions were noted in the hard medium specimens but these probably were not significant. In the aerobic studies the organisms were more of the coliform types, they being identified as *Eberthella douglasi*, *dispar* and *pritznitsi* and *Escherichia coagulans*, *wesenbergi* and *coli*. These all phaged within three days. In one case a nonhemolytic streptococcus came in on the third day, remaining only about twenty-four hours. Beginning about the fourth day in both cases and persisting for two weeks, when the observations were discontinued, *Staphylococcus albus* became prominent, and there is reason to believe that this organism was important in an etiologic sense. What was interesting was that *Staphylococcus albus* was noted only in the aerobic tubes.

#### CONCLUSIONS

A type of chronic peritonitis was observed that has not been described in an extensive search of the literature.

Apparently the cases are not common and are characterized by continued illness of a most persistent painful type, the absence of constitutional symptoms and the presence of a fair state of health.

The bacteriology of the peritoneal cavity seems to be of the mixed type in which *Staphylococcus albus* is prominent and this seems to be important in an etiologic way.

The improvement clinically in the second case and the improvement in the appearance of the peritoneum between the operations in the third case suggest that the improvement came about by the fistula, which in each case was large enough to be practically equivalent to an ileostomy. If this constant drainage of the small intestine brought about the benefits, it seems logical to suppose that when this type of chronic peritonitis is encountered at operation, instead of attempting to do various types of operations, it would be wiser to perform an ileostomy at once and perhaps one of the closure types of anastomoses at from six to twelve months afterward.

121 East Seventy-First Street.

**Three Varieties of Lice.**—The louse attaches its eggs either to hair or to fabric by an insoluble cement. The female lays five or more such eggs daily, and, since the nit hatches in eight days and is full grown in a month, a single female may have thousands of descendants in a few weeks. The provision for the birth of the young louse is unique. One end of the egg has a cap, which is pierced by holes. When ready to emerge, the young louse swallows air, which, when ejected from the bowel, produces enough pressure to force its body out of the egg. There are three varieties of lice parasitic to man: *Pediculus capitis* or head louse, *Pediculus vestimenti* or body louse, and *Pediculus pubis* or crab louse.—Holmes, William H.: *Bacillary and Rickettsial Infections*, New York, Macmillan Company, 1940.

## Clinical Notes, Suggestions and New Instruments

### CONTACT DERMATITIS DUE TO NAIL POLISH

FRANCIS A. ELLIS, M.D., BALTIMORE, AND HAYDEN KIRBY-SMITH, M.D., WASHINGTON, D. C.

Contact dermatitis due to nail polish probably is more common than the number of reported cases indicates. The 5 cases reported here illustrate the necessity for considering nail polish as a cause of dermatitis on the eyelids, face, neck and arms. Even though the patient has used the polish for years with impunity, it may still be the contact irritant.

Silver and Chiego<sup>1</sup> attempted to sensitize guinea pigs to nail lacquers without success. Five thousand patch tests with nail lacquers and various constituents of the finished product resulted in negative reactions to the finished enamels and some plus-minus to "1 plus reactions" to certain dyes. They suggested that the other ingredients protected the skin from the dyes. Silver and Chiego found the report of only 1 case on nail lacquer dermatitis, but from the random statements in the literature they inferred that nail lacquers are possible causative agents for various types of eruptions. Schwartz in discussing contact dermatitis mentions the fact that many cases of dermatitis due to nail polishes are seen. Schwartz and Tulipan<sup>2</sup> state that dermatitis of the face has been reported from contact with finger nails dressed with nail polish. Rostenberg and Sulzberger<sup>3</sup> and Sulzberger<sup>4</sup> state that patch tests may be made with nail polish at the concentration in the original container.

Sulzberger has reported 2 cases of dermatitis due to nail polish. The first<sup>5</sup> was that of a girl who had an eruption in the axillary fossae and on the neck due to a red dress. Later three attacks of dermatitis on the face and eyelids followed an application of a red nail polish. A patch test with a red lipstick gave a negative reaction and the patient was able to use with impunity nail polish of a different make. In the second case<sup>6</sup> the eruption involved eventually the eyelids, lips, face, neck, chest and arms. After the eruption had undergone involution a patch test with the nail polish resulted in a local reaction and a flare-up of dermatitis in the previously affected areas.

Belote<sup>7</sup> stated that it is surprising how many eruptions around the eyes and nose are actually due to nail polish and nail polish remover. Feiler<sup>8</sup> reported a case of dermatitis of the face of a patient whose skin was sensitive to Almay perfume, Style-set lipstick and Platinum nail polish.

#### REPORT OF CASES

**CASE 1.**—L. V. S., a white girl aged 24, was seen for a dermatitis of five months' duration which had appeared first on the face and neck and later in the cubital spaces. Two months after the original eruption some irritation appeared on the dorsum of the fingers over the terminal phalanx just proximal to the nail folds. The eruption was essentially the same in all areas and consisted of an ill defined erythema with some evidence of mild vesiculation and a slight, loosely adherent scaling. The dermatitis on the finger tips was very suggestive that nail polish was acting as an irritant, in spite of the fact that eruption on the other parts had appeared two months previously. She gave a positive reaction to a patch test of a certain nail polish which she had been using but a negative

1. Silver, Henry, and Chiego, Bernard: Nails and Nail Changes: Investigation of Nail Lacquers and Their Components, *J. Invest. Dermat.* 2: 361 (Dec.) 1939.

2. Schwartz, Louis, and Tulipan, Louis: A Text-Book of Occupational Diseases of the Skin, Philadelphia, Lea & Febiger, 1939, p. 238.

3. Rostenberg, Adolph, Jr., and Sulzberger, M. B.: A List of Substances for Patch Testing and Concentrations to Be Employed, *J. Invest. Dermat.* 2: 93 (June) 1939.

4. Sulzberger, M. B.: *Dermatologic Allergy*, Baltimore, C. C. Thomas, Publisher, 1940, p. 437.

5. Sulzberger, M. B.: Hypersensitivity to Nail Polish, *Arch. Dermat. & Syph.* 36: 460 (Aug.) 1937.

6. Sulzberger, M. B.: Eczema Venenatum from Nail Polish, *Arch. Dermat. & Syph.* 42: 218 (July) 1940.

7. Belote, G. H., in discussion on Eczema Seborrhoeicum with Unusual Persistent Localization, *Arch. Dermat. & Syph.* 41: 1121 (June) 1940.

8. Feiler, H. B.: Eczema Venenatum Due to Lipstick and Nail Polish, *Arch. Dermat. & Syph.* 42: 224 (July) 1940.

reaction to nail polish remover. Control tests on two normal persons gave negative results. The patient discontinued the use of this nail polish and with mild local therapy the condition practically disappeared in about two weeks. In response to an inquiry the makers of the offending polish wrote that their various shades of nail enamels contained in all about eighty possible ingredients. Through Dr. Louis Schwartz of the National Institute of Health we obtained some of these ingredients and made patch tests with "plasticizers," castor oil, camphor, dibutylphthalate and also with clear lacquer, titanium dioxide and several of the dyes, including oil orange F, D and C number 2, deep maroon c24004, tropical red D and C number 8 and barium lake red. There was a slightly positive reaction to deep maroon c24004 and to the camphor plasticizer and a strongly positive (vesiculation) reaction to clear lacquer. The other tests gave negative results.

CASE 2.—A white girl aged 19 was first seen on June 3, 1940, for an eruption of two months' duration. The eruption was on the lobes of the ears, on the chin, on the alae of the nose, on and around the eyelids, on the anterior axillary folds and on the extensor surfaces of the thumbs just proximal to the nail borders. It consisted of ill defined areas of acute and subacute dermatitis whose essential characteristics were moderate erythema, slight vesiculation, exudation or weeping and the presence of varying amounts of crusts and scales. The patient complained of marked pruritus. A definite etiologic factor was not determined; nevertheless the dermatitis responded to local external therapy. One month later the patient returned because of an exacerbation of the eruption in the majority of the areas formerly affected. Patch tests were made with several types of perfumes, a nail polish and a nail polish remover. All gave negative results except the nail polish. This caused a "2 plus" reaction which was moderately active ten days later. The presence of the severe dermatitis on the lobes of the ears was partly explained by the fact that the patient wore ear rings, and in the process of putting them on the nail surfaces came in contact with this part of the ear.

Patch tests were performed with "plasticizers," castor oil, camphor, dibutylphthalate, clear lacquer, titanium dioxide and a second nail polish, with negative reactions to all but the finished nail polish. The tests demonstrate that the ingredients of the foundation of the nail polish tested did not protect the patient to the finished polish or the dye.

CASE 3.—M. C., a white woman aged 22, was referred to us for diagnosis and treatment of a moderately pruritic eruption of one month's duration on the left palm and about the eyes. The eruption began on the left palm, and a few days later an area around the eyes became involved. An ointment and a lotion prescribed by her family physician apparently aggravated the condition.

The left palm presented a well defined 2.5 by 2 cm. oval patch consisting of grouped and confluent erythematous deep seated vesicles about 2 mm. in diameter. In some areas there was slight scaling and crusting. On the eyelids, extending slightly above the eyebrows and on the infra-orbital region, there was an ill defined, erythematous, edematous, slightly scaly eruption. Examination of the feet and toes for evidence of fungous infection revealed only a slight fissuring in the interphalangeal web of the fourth and fifth toes of the right foot. The dermatitis of the eyelids had features strongly suggestive of an eruption of contact origin. Therefore patch tests were performed with the ointment and lotion previously used and with another brand of nail polish and remover. There was a very marked vesicular reaction to the ointment, the nail polish and the polish remover. Two control patients gave a strongly positive reaction to the ointment, thus indicating if not proving that it was a primary irritant. The eruption of the eyelids showed marked improvement following the application of a mild lotion and the removal of all irritants. Later patch tests were performed with three other brands of nail polish, clear lacquer, dibutylphthalate, castor oil, camphor and titanium dioxide. The results were a mild positive reaction to dibutylphthalate and a plus-minus reaction to clear lacquer. The patient refused further patch testing. It is of interest that the patient had used the nail polish and polish remover for a number of years with impunity and only

after an ointment had caused an irritation about the eyes did she apparently become sensitive to the nail polish and polish remover.

CASE 4.—A white woman aged 29, first seen on March 7, 1940, presented an eruption on the neck and face. The lesion was of three weeks' duration and had the characteristics of a dermatitis of external contact origin. The first site involved was the anterior part of the left side of the neck. The dermatitis then spread to the orbital region. Patch tests with various materials suggested by the history failed to determine the etiologic factor. Subsequently the eruption extended to her shoulder. When the patient was seen on July 1 she had two areas of dermatitis on her legs corresponding to the areas of her stocking to which she had applied a nail polish two days previously for "runs." Patch tests were made with a colorless nail polish and three other brands of tinted nail polish. All four gave positive results. There was no reaction to a patch test with titanium dioxide and the three plasticizers, but there was a "4 plus" reaction to the clear lacquer. Control patch tests on a normal person were negative.

CASE 5.—A white woman aged 30 on May 13, 1940, noticed a swelling, redness and itching on the upper eyelids and on the lower lip below the vermilion border. After several periods of quiescence and exacerbations the patient stopped the use of all cosmetics. When the dermatitis had disappeared the use of cosmetics was resumed by applying a new preparation every two days. Twelve hours after a nail polish was painted on the nails the eruption reappeared on the eyelids and the lower lip. Later when another brand of nail polish was applied the redness and pruritus recurred. The fingers were not affected. Patch tests with the three plasticizers, titanium dioxide and clear lacquer gave negative results. This indicated that the dye was the sensitizing agent.

#### COMMENT

Considering the widespread use of nail polish and the few reports of dermatitis due to this cosmetic, one would infer that nail polish is a relatively unimportant etiologic factor of contact dermatitis. It is recognized that any of its ingredients may act as a sensitizer, but our experience suggests that the more important factors are the clear lacquer and the dyes. Three patients gave positive reactions to the clear lacquer. This is cellulose nitrate dissolved in a mixture of volatile solvents. The volatile solvents are usually primary irritants<sup>11</sup> because they are fat solvents capable of dissolving the sebaceous material, or fat, of the skin. However, when applied, covered with cellophane or uncovered, five control patch tests with the lacquer gave negative results. The dye in many of our cases was probably the responsible agent because the other ingredients usually gave negative reactions. The clear lacquer may have the property of synergic or potentiating antigenicity;<sup>12</sup> briefly, this means that when the clear lacquer is mixed with another antigen it enhances or changes the antigenicity of the second substance (the dye). Case 3 may be another example of this phenomenon. The dermatitis, which was due to another cause, apparently initiated sensitization to nail polish and remover. It is well recognized that persons with fungous, bacterial, atopic or contact dermatitis are prone to become sensitized to agents which they previously used with impunity. The second and fifth cases demonstrate that the ingredients in the foundation do not necessarily protect the patient from the finished product containing a dye even though negative reactions are obtained to the ingredients of the foundation of the nail polish.<sup>13</sup>

#### SUMMARY

1. Nail polish probably is more frequently the cause of contact dermatitis than may be implied from the few previously reported cases.

9. Dr. Maurice Sullivan gave the authors permission to report this case.

10. Drs. Maurice Sullivan and Robert Arthur gave the authors permission to report this case.

11. Schwartz, Louis: Personal communication to the authors.

12. Burky, Early, in discussion on Dermatitis of the Hands, Arch. Dermat. & Syph. 39: 893 (May) 1939.

13. Since this article was accepted for publication we have seen 4 additional patients with dermatitis on the face due to nail polish. All gave positive patch tests to a finger nail polish in contrast to those reported by Lester Hollander (Nail Lacquer Dermatitis, J. A. M. A. 115: 1714 [Nov. 16] 1940).

2. The dyes and/or the foundation of a nail polish may be the sensitizing agent.

3. A patient sensitized to one brand of nail polish at times may use with impunity another brand of polish or the same brand containing a different dye.

5. The eruptions due to nail polish usually appear first on the eyelids and in the cubital spaces. The surface of the finger near the nail may not show any dermatitis. This could be due to the protective quality of their thick epidermal coverings.

8 East Madison Street—1610 Twentieth Street N.W.

## Special Article

### GLANDULAR PHYSIOLOGY AND THERAPY

#### GONADOTROPINS OF THE ANTERIOR LOBE OF THE PITUITARY AND OF CHORIONIC TISSUE

EARL T. ENGLE, PH.D.

AND

LOUIS LEVIN, PH.D.

NEW YORK

*This special article is published under the auspices of the Council on Pharmacy and Chemistry. It is one of a series which will be published in book form as the second edition of "Glandular Physiology and Therapy." The opinions expressed in this article are those of the authors and do not necessarily represent the views of the Council.—Ed.*

The concept of gonadotropic action of the anterior lobe of the pituitary gland arose from the experiments of Philip E. Smith in 1926, in which the treatment of immature rodents with implants of fresh anterior lobe produced follicular growth and the formation of corpora lutea. Similar effects were found at the same time in immature mice by Aschheim and Zondek, but Smith demonstrated that atrophy of the gonads follows hypophysectomy and that it may be prevented or the gonads repaired by treatment with fresh anterior pituitary implants.

Since this pioneer work, an amazing mass of literature concerning this subject has accumulated. It is beyond the scope of this chapter to consider all the work which has been reported. For such a comprehensive review the reader is referred to Van Dyke (1939).<sup>1</sup> In the present article attention will be directed to those observations which appear to be most firmly established and of greatest interest to one seeking to understand the action of the gonadotropic substances.

#### CLASSIFICATION

Two large groups of gonadotropins, differing in their qualitative physiologic action, are now known. The first consists of those obtained directly from the pituitary gland and, in addition, those probably of pituitary origin extracted from the blood and urine of normal men and women and of women who have undergone menopause (artificial or natural).

The second major group of gonadotropins, the chorionic, derives its name from the fact that these substances are found in body fluids and tissues in the

presence of living chorionic tissue, i. e., during normal pregnancy in women and in mares or when pathologic chorionic tissue is present. It is an accepted opinion that these gonadotropins originate from chorionic cells and are not anterior pituitary gonadotropins.

#### ANTERIOR PITUITARY GONADOTROPINS

Several gonadotropins from the anterior lobe of the pituitary have been postulated, but there is no general agreement as to their identity or their action. The greatest unanimity of opinion probably exists with respect to the so-called follicle-stimulating and luteinizing hormones, first postulated by Zondek, but the evidence as to the separate identity of these is not completely convincing to all investigators.

A great deal of the disagreement concerning the occurrence of these two gonadotropins as separate entities is due to the fact that at present proof of the identity of either substance depends on biologic differentiation. This differentiation is, in turn, complicated by lack of distinct end points. In many reports the interpretation of qualitative results is further complicated by the fact that intact animals were used, thus introducing as a factor the variable and unpredictable participation of the animal's own pituitary. Only the hypophysectomized rat or mouse affords standard test conditions.

The present status of the so-called follicle-stimulating and luteinizing hormones may be briefly summarized as follows:

A number of reactions of the ovaries and of the testes have been ascribed to each of these hormones. In the hypophysectomized female rat the purified follicle-stimulating extract causes growth and development of numerous follicles, associated with increase in ovarian weight. According to proponents of the dual hormone theory, it does not, if completely separated from the luteinizing factor, produce any lutein changes.

A secondary effect of the follicle-stimulating factor, presumably due to secretion of estrogen by the developing follicles, is the development of the secondary genitalia. However, Greep, Van Dyke and Chow (1940)<sup>2</sup> have recently described what is claimed to be a very pure preparation of the follicle-stimulating substance and have stated that although it stimulates follicular growth, it does not have any estrogenic effect, as indicated by lack of uterine and vaginal change.

When administered to the hypophysectomized male rat, the follicle-stimulating extract produces a reaction analogous to that in the female. The epithelium of the seminiferous tubules is maintained or repaired, and sperm formation proceeds at least to the stage at which secondary spermatocytes appear. There is no effect on the testicular interstitial tissue, which remains atrophic, as indicated by its histologic appearance as well as by the atrophic state of the accessory sex glands.

The identity of the luteinizing hormone is particularly difficult to establish when its effects on the ovary are studied. According to proponents of the dual hormone theory, the luteinizing factor by itself has no positive effect on the ovary of the hypophysectomized rat. Follicles ripened to a certain degree are apparently necessary for the production of lutein changes by the luteinizing hormone. Such changes may be produced

From the Department of Anatomy, College of Physicians and Surgeons, Columbia University.

1. Van Dyke, H. B.: *The Physiology and Pharmacology of the Pituitary Body*, Chicago, University of Chicago Press, 1936, vol. 1; 1939, vol. 2.

2. Greep, R. O.; Van Dyke, H. B., and Chow, B. F.: Separation in Nearly Pure Form of Luteinizing (Interstitial-Cell-Stimulating) and Follicle-Stimulating (Gametogenic) Hormones of the Pituitary Gland, *J. Biol. Chem.* **133**: 289 (March) 1940. Shedlovsky, T.; Rothen, A.; Greep, R. O.; Van Dyke, H. B., and Chow, B. F.: The Isolation in Pure Form of the Interstitial Cell-Stimulating (Luteinizing) Hormone of the Anterior Lobe of the Pituitary Gland, *Science* **92**: 178 (Aug.) 1940.



by administering an extract containing the latter factor to animals simultaneously with, or following, an extract containing the follicle-stimulating factor, in which case luteinization and sometimes ovulation result. The combination of the luteinizing and follicle-stimulating extracts also results in the "augmentation" phenomenon, the weight of the ovary increasing much beyond the sum of the increases produced by the two substances separately. It is stated<sup>3</sup> that the luteinizing hormone stimulates the interstitial ovarian tissue.<sup>4</sup> Another action of this hormone is that of causing rapid involution of existing corpora lutea with concomitant decrease in ovarian weight.<sup>5</sup> The absence of this hormone may be the reason for the prolonged survival of preformed corpora in the hypophysectomized rat.

In the hypophysectomized male rat the luteinizing extract is reported to have a more distinct effect. Whereas in this form the follicle-stimulating substance stimulates only the tubular elements of the testis, the luteinizing factor produces growth and functional activity of the interstitial cells, as indicated by the histologic picture of the testis, as well as by the growth and development of the accessory sex glands, presumably as a result of secretion of androgen. If male rats are treated with a combination of follicle-stimulating and luteinizing substances, a synergism between the activities of these substances is noted, the responses being greater than with either fraction alone.<sup>6</sup>

Evidence has been offered enabling several authors to question the identity of two distinct pituitary gonadotropins or of a separate luteinizing factor. This evidence, beginning with the findings of Maxwell (1934)<sup>7</sup> is based on the fact that by manipulating the rate at which the administered gonadotropin reaches the ovary the reactions ascribed to the luteinizing factor by its proponents may be abolished or caused to appear. Thus Maxwell and others have demonstrated that by properly dividing the doses of unfractionated pituitary extract to be administered the incidence of lutein changes may be greatly diminished. Also, it has been adequately shown that addition of zinc sulfate ( $ZnSO_4$ ) or copper sulfate ( $CuSO_4$ ) or a variety of other nonspecific substances to the unfractionated extract causes at least partial abolition of the luteinizing properties. All these treatments tending to decrease the rate of entrance of the injected gonadotropin into the blood stream also increase the weight response of the ovary. Furthermore, Saunders and Cole<sup>8</sup> have reported that zinc sulfate and egg albumin, if combined with the follicle-stimulating extract, are more effective in producing augmentation than is the luteinizing substance. However, it should be pointed out that the follicle-stimulating

substance (and/or synergist<sup>9</sup>) which was used by these authors, of itself, produced corpora lutea in a great majority of the treated animals. It is not surprising, therefore, that addition of more luteinizing substance failed to produce augmentation.

The increased weight response and the decrease in the incidence of luteinization which result when the rate of entrance of the gonadotropin into the blood stream is decreased by the addition of nonspecific substances have been demonstrated only in the female rat. In these instances nonspecific substances have been substituted for luteinizing substance. However, the luteinizing fraction alone will cause interstitial activation in the male, and no one has yet demonstrated that nonspecific substances alone are able to simulate the effects of luteinizing substance on the interstitial cells and accessory sex glands of the hypophysectomized male rat.

Other evidence cited in support of the two hormone theory is that produced by Du Shane and his associates.<sup>10</sup> These investigators, using parabiotically united rats, castrated one of the parabionts (either male or female) and hypophysectomized the other (female). The ovaries of the hypophysectomized partner showed a high degree of follicular stimulation over a long period. They contained large follicles, many of them cystic, but no lutein changes were present. This correlates well with the concept that after castration the pituitary secretes large amounts of follicle-stimulating hormone. If there is only one pituitary gonadotropic hormone, it is not easily understandable why such ovaries, apparently exposed to effective gonadotropic stimulation over long periods, do not show lutein changes.

On the other hand, experiments have been performed that were identical except that hypophysectomized male instead of female rats were exposed to the gonadotropin from castrate parabiotic partners.<sup>11</sup> In these experiments the testes showed maintenance of interstitial cells and of accessory glands, a reaction presumably evoked by the luteinizing rather than by the follicle-stimulating hormone. Similarly Greep<sup>12</sup> simultaneously produced parabiosis of a hypophysectomized immature male rat, on one hand, and of a hypophysectomized female rat, on the other, with a third rat, a castrate. Thus a pair of testes and a pair of ovaries were simultaneously subjected to the same gonadotropin in identical dosage. Development of all the testicular elements was noted, while the ovaries showed only follicular stimulation.

The findings of Rowlands<sup>13</sup> are also interpreted to indicate two gonadotropic hormones. He treated rabbits chronically with preparations rich in luteinizing potency until antigonadotropic substances were demonstrable in the serums. These serums when injected together with unfractionated extracts containing both the follicle-stimulating and the luteinizing factor were able to neutralize selectively the luteinizing factor, leaving the

3. (a) Evans, H. M.; Simpson, M. E., and Pencharz, R. I.: An Anterior Pituitary Gonadotropic Fraction (Interstitial-Cell-Stimulating) Specifically Stimulating the Interstitial Tissue of Testis and Ovary, Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1937, vol. 5. (b) Fevold, H. L.: Extraction and Standardization of Pituitary Follicle-Stimulating and Luteinizing Hormones, *Endocrinology* 24: 435 (April) 1939.

4. Evans, Simpson and Pencharz have claimed the separation of an additional gonadotropin which stimulates only the interstitial cells of the ovary and testis. This material, named interstitial cell-stimulating hormone, appears to be the same as the previously postulated luteinizing factor. Evans, H. M.; Simpson, M. E.; Toksdorf, Sybille, and Jensen, R. O.: *Endocrinology* 24: 435 (April) 1939. Fevold, H. L.: *Endocrinology* 24: 435 (April) 1939.

5. Greep, R. O.: The Effect of the Male Gonad, in Cold Spring Harbor Symposium on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1937, vol. 5.

6. Greep, R. O.: The Effect of the Male Gonad, in Cold Spring Harbor Symposium on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1937, vol. 5.

7. Maxwell, R. L., and Cole, H. H.: On the Reliability of Present Methods for the Assay of Gonadotropic Hormones, *Follicle-Stimulating and Luteinizing Hormones*, 23: 302 (Sept.) 1938.

9. The designation of the "synergist" as a separate and distinct gonadotropic fraction no longer seems justified since Evans has admitted that the pituitary fraction designated by this term is the same as the follicle-stimulating fraction.

10. Du Shane, G. P.; Levine, W. T.; Pfeiffer, C. A., and Witschi, E.: Experimental "Constant Oestrus" and the Notion of Antigonadotropic Hormones, *Proc. Soc. Exper. Biol. & Med.* 33: 339 (Dec.) 1935.

11. Cutuly, Eugene; McCullagh, D. R., and Cutuly, Elizabeth: The Type and Degree of Gonadal Stimulation Induced in Hypophysectomized Male Rats Parabiotically Joined with Castrated, Cryptorchid, and Normal Partners, *Endocrinology* 21: 241 (March) 1937. Cutuly, Eugene and Cutuly, Elizabeth C.: Inhibition of Gonadotropic Activity by Sex Hormones in Parabiotic Rats, *ibid.* 22: 568 (May) 1938.

12. Greep, R. O.: Pituitary Function in Parabiotic Triplet Rats, *Proc. Soc. Exper. Biol. & Med.* 44: 214 (May) 1940.

13. Rowlands, I. W.: Selective Neutralization of the Luteinizing Activity of Gonadotropic Extracts of Pituitary by Anti-Sera, *Proc. Roy. Soc., London, s. B* 126: 76 (Sept. 23) 1938.

follicle-stimulating one free to act. That this was not a matter of alteration of the rate of absorption of a gonadotropin by nonspecific substances was proved by the fact that serums from control animals did not possess this selective neutralizing ability. Furthermore, the selective inactivation was observed after injection of serum and gonadotropin at different sites, so that mixing, if any, presumably occurred after absorption.

A great deal of chemical work has been done on the separation of the two hormones (Fevold;<sup>14</sup> Evans;<sup>15</sup> Wallen-Lawrence;<sup>16</sup> Van Dyke<sup>17</sup>). Many of the preparations have been considerably purified, and data to indicate chemical homogeneity have been reported for at least one preparation.<sup>2</sup> Selective inactivation by enzymatic action has been employed to demonstrate the presence of two separate gonadotropic substances. However, in every case the demonstration of the distinctness of the hormone fractions has depended on one or more of the biologic tests described in foregoing paragraphs. Until the qualitative accuracy of the biologic end points have been more adequately demonstrated and until the luteinizing hormone-like effects of nonspecific substances are completely ruled out, it is not profitable, in relation to this question, to discuss the chemical differences which have been reported for the two fractions.

It has not been adequately shown that the best preparations of the follicle-stimulating and the luteinizing factor so far reported, if injected in high doses or over long periods, will not each produce the effects ascribed to the other. The difficulty of a distinct chemical separation of this type of substance makes understandable the contamination which occurs in even the best preparations made to date. It must be recognized, however, that the final solution of this problem will be achieved only when one or more active substances have been isolated in chemically pure form and when it is demonstrated whether one or more of the pure substances are necessary to account for all the physiologic responses. It may be hoped that the chemically pure luteinizing hormone announced by Shedlovsky and his co-workers<sup>2</sup> will soon lead to such a demonstration.

In summary, the validity of the concept of two distinct pituitary gonadotropins depends at present chiefly on proof of the occurrence of the so-called luteinizing hormone. Proof based on the reactions of the rodent ovary is inadequate because similar reactions can be produced by manipulation of dosage and by use of nonspecific substances. The reaction of the testis affords better indications of the occurrence of a gonadotropic principle distinct from the follicle-stimulating or gametokinetic hormone, but even in this regard one encounters valid conflicting evidence. Therefore, a final answer to this important and intriguing question must await further clarifying work.

14. Fevold, H. L.: The Gonadotropins. In Cold Spring Harbor Symposia on Quantitative Biology, New York, The Biol. Sec., 1939. Vol. 1, p. 1. Lee, M.; Hisaw, F. L.: The Physiology of the Anterior Pituitary Gland. New York, McGraw-Hill, 1940. Fevold<sup>2b</sup>

15. Jensen, H.; Simpson, Miriam E.; Tolksdorf, Sybille, and Evans, H. M.: Chemical Fractionation of the Gonadotropic Factors Present in Sheep Pituitary. *Endocrinology* 25:57 (July) 1939. Evans, H. M.; Korp, K.; Simpson, M. E.; Pencharz, R. I., and Wonder, D. H.: On the Separation of the Interstitial Cell-Stimulating, Luteinizing and Follicle-Stimulating Fractions of the Anterior Pituitary Gonadotropic Complex. *Univ. California Publ. Anat.* 1:255, 1936.

16. Wallen-Lawrence, Zonja: Proof of the Existence of a Follicle-Stimulating and a Luteinizing Hormone in the Anterior Lobe of the Pituitary Body. *J. Pharmacol. & Exper. Therap.* 51:263 (July) 1934.

17. Chow, B. F.; Greep, R. O., and Van Dyke, H. B.: The Effects of Digestion by Proteolytic Enzymes on the Gonadotropic and Thyrotrophic Potency of Anterior Pituitary Extract. *J. Endocrinol.* 1:440 (Dec.) 1939. Greep and others.<sup>2</sup>

## URINARY GONADOTROPINS

Considerable quantities of a gonadotropin are present in the blood and urine of ovariectomized (Fluhman) and postmenopausal (Zondek) women. The work of Hamburger<sup>18</sup> demonstrated this substance to be qualitatively different from the chorionic gonadotropin excreted by pregnant women. Experiments performed with extracts of relatively low potency led Smith and Engle, and Smith, Engle and Tyndale to consider this material as containing a follicle-stimulating or gametokinetic factor. More recently Tyndale, Levin and Smith<sup>19</sup> studied the effects of more potent and relatively nontoxic extracts of this gonadotropin. Normal and hypophysectomized immature rats were used. In the latter the extracts produced only follicular stimulation over a wide dose range. However, when larger doses, eight to ten times the minimal stimulating dose, were administered, luteinization was observed in all the animals. This material, like the pituitary follicle-stimulating substance used by others, produces luteinization if enough of it is administered.

The results obtained when the same material was administered to intact immature rats afford an interesting comparison. Throughout the dose range corpora lutea were formed in the ovaries of some but not all of the test animals. The proportion of animals showing corpora increased with increased dose until, at precisely that dose which produced luteinization in the hypophysectomized animals, all the normal animals showed corpora in their ovaries. This indicates the role which the animal's own pituitary (even before sexual maturity) may play in the gonadotropic-gonadal relationship and the care which consequently must be exercised in the interpretation of qualitative results obtained by the use of intact animals.

That women with normal ovarian function excrete small amounts of a gonadotropin for a short time during the midinterval has been shown.<sup>20</sup> More recently Werner,<sup>21</sup> using the sensitive mouse uterus assay method,<sup>22</sup> has been able to show that this gonadotropin is excreted in a demonstrable amount throughout the menstrual cycle and that the amount is quite constant except for a sudden transient increase during the midinterval. This transient rise, probably related to the ovulatory process, is responsible for the occasional period of excretion noted by the earlier investigators, who used less sensitive assay methods and possibly less quantitative concentration procedures. Werner, in certain of his studies, also determined the excretion of pregnandiol and found that this substance, an indicator of progesterone secretion by the corpus luteum, frequently appears in the urine within two to five days after the "ovulatory" increase in gonadotropin excretion.

18. Hamburger, Christian: Studies on Gonadotropic Hormones from the Hypophysis and Chorionic Tissue, with Special Reference to Their Differences. *Acta path. et microbiol. Scandinav.*, 1933, supp. 17.

19. Tyndale, H. H.; Levin, Louis, and Smith, P. E.: Responses of Normal and Hypophysectomized Immature Rats to Menopausal Urine Injections. *Am. J. Physiol.* 124:174 (Oct.) 1938.

20. Kurzrok, Raphael; Kirkman, Irene J., and Creelman, Margaret: Studies Relating to the Time of Human Ovulation. *Am. J. Obst. & Gynec.* 28:319 (Sept.) 1934. Frank, R. T., and Salmon, U. J.: Gonadotropic Blood and Urine Cycles in Normal Menstruating Women. *Proc. Soc. Exper. Biol. & Med.* 32:1237 (May) 1935. Smith, G. V., and Smith, O. W.: The Urinary Excretion of Estrogenic and Gonadotropic Hormones During Menstrual Cycles, the Period of Conception and Early Pregnancy. *New England J. Med.* 215:908 (Nov. 12) 1936. D'Amour, F. E.; Funk, Dorothy, and Liverman, Helen: Daily Gonadotropic Hormone Tests During Fifty Complete Menstrual Cycles. *Am. J. Obst. & Gynec.* 37:940 (June) 1939.

21. Werner, S. C.: A Quantitative Study of the Urinary Excretion of Hypophyseal Gonadotropin, Estrogen and Androgen of Normal Women. *J. Clin. Investigation*, to be published.

22. Levin, Louis, and Tyndale, H. H.: The Quantitative Assay of "Follicle-Stimulating" Substances. *Endocrinology* 21:619 (Sept.) 1937.



Although the exact nature of the gonadotropin excreted by normal women is not yet established, a limited study by D'Amour<sup>23</sup> indicates that this substance is very similar to that excreted following the menopause.

Normal men excrete a gonadotropin in somewhat larger amounts than do normal women. No careful day by day studies have been made, but the available data afford no indication of cyclic variation in this excretion.

The qualitative nature of the urinary gonadotropin of the normal male has been investigated recently in this laboratory.<sup>24</sup> Over a wide dose range this material produced only follicular stimulation in immature hypophysectomized female rats. Higher doses caused lutein changes. It therefore appears that the urinary gonadotropin of normal men is very similar to or identical with that excreted by ovariectomized or postmenopausal women.

It is of interest that although postclimacteric women excrete increased amounts of gonadotropin with fair regularity, several investigators have been unable to find increased excretion of gonadotropin in aged men with varying degrees of genital involution.

#### GONADOTROPIN OF HUMAN PREGNANCY

The gonadotropin of human pregnancy was discovered by Aschheim and Zondek. It appears in the blood and urine soon after the implantation of the egg,<sup>25</sup> and affords the basis for the Aschheim-Zondek and Friedman pregnancy tests. It has been reported to appear before the first missed menstrual period. The concentration of the gonadotropin in the blood and urine increases rapidly during the first part of pregnancy, reaching a high titer fifty to sixty days after the last menstrual period; it then declines rapidly to relatively low levels, which are maintained until a few days after parturition, when the substance disappears from the blood and urine. The same gonadotropin has been demonstrated in large amounts in the placenta, the concentration being roughly parallel to that in the blood and urine.

A gonadotropin has also been found during brief periods in the urine of pregnant rhesus monkeys and chimpanzees. A similar but not identical chorionic gonadotropin, to be discussed in a later section of this review, appears in the blood but not the urine of pregnant mares. Investigation of the tissues and body fluids of a rather extensive variety of other mammals has not as yet demonstrated gonadotropic activity.

The human chorionic gonadotropin differs qualitatively from other known gonadotropins. It is not anterior pituitary-like, and there is no longer any reason for the use of the designation "anterior pituitary-like," which was applied to this gonadotropin before its nature was well known. Neither is the designation "prolan A" as defined by Zondek any longer applicable to any fraction of this substance, since it is not under any condition a follicle-stimulating gonadotropin.

In the immature female rodent (rat or mouse) the growth of follicles (reaction 1), the appearance of hemorrhagic follicles (reaction 2, more constant in the mouse) and the formation of corpora lutea (reaction 3)

follow exactly the description recorded by Aschheim and Zondek. Examination of the effects of this gonadotropin in the hypophysectomized rat prove that these reactions, though valid for the intact animal, are partially due to the participation of the animal's own pituitary. The age of the animal and the length of the period of regression following removal of the pituitary both affect the quality of the response.

In immature female rats treated immediately after hypophysectomy Leonard and Smith<sup>26</sup> found that corpora lutea could be formed. This occurs only if maturing follicles are present in the ovary at the time of hypophysectomy and if treatment is instituted immediately. In either case the interfollicular (interstitial) cells as well as the cells of the theca are caused to hypertrophy, and atretic follicles are converted into luteoid bodies. Estrogen is secreted (by the hypertrophied interstitial and thecal cells), as indicated by the vaginal cornification and estrus. In no instance has human chorionic gonadotropin been observed to cause follicular growth in hypophysectomized animals, whether adult or immature.

In general, all other animals below primates which have been studied react as does the rat. Details of the species differences can be found elsewhere.<sup>25</sup> In the presence of a functional hypophysis, treatment with this chorionic gonadotropin results in stimulation of follicles and luteinization, frequently with ovulation. If the hypophysis is removed, estrus is induced by the secretion of the interfollicular, interstitial or thecal cells without follicular growth.

The Algerian baboon is reported to respond as do the lower animals (Courrier). The common laboratory rhesus monkey (*Macacus mulatta*), however, is quite different. Even in intact monkeys (rhesus) the human chorionic gonadotropin causes neither follicular growth, nor ovulation nor luteinization. If normal animals in the first part of the menstrual cycle are given adequate doses of an extract containing this substance, the estrogenically induced swelling and color of the sex skin disappears and the bleeding due to estrogen withdrawal follows. In immature females no follicular stimulation occurs, as judged by either the sex skin response or by ovarian structural changes. Small follicles are quickly forced into atresia with the formation of scar tissue, similar to corpora albicantia. Corpora lutea may be formed in the intact animal if a follicle stimulator is added to the chorionic gonadotropin.

Geist reported on structural changes in human ovaries after treatment with human chorionic gonadotropin and stated that "apparently there is no stimulation of the follicle, rather an arrest of follicular development." Hamblen,<sup>27</sup> in several series, observed neither follicular growth, nor ovulation nor production of functional corpora lutea. That the structural changes of the human ovary after this treatment are mainly those of arrest or are degenerative in nature does not necessarily indicate that this substance is therapeutically without value in women.

The therapeutic value of this substance in gynecologic practice will be discussed in another chapter. It is pertinent to state here, however, that morphologic studies on human ovaries conform in general to the observations on the monkey.

23. D'Amour, F. E.: *A Qualitative Study of Normal Gonadotropin*, *Am. J. Physiol.* 127: 649 (Nov.) 1939.

24. Leatham, J. H., and Levin, Louis: *The Gonadotropic Action of Normal Male Urine Extract on the Ovaries of Normal and Hypophysectomized Immature Rats and of Immature Mice*, to be published.

25. Engle, E. T.: *Gonadotropic Substances of Blood, Urine and Other Body Fluids*, in Allen, Edgar; Danforth, C. H., and Doisy, E. A.: *Sex and Internal Secretions*, Baltimore, Williams & Wilkins Company, 1939.

26. Leonard, S. L., and Smith, P. E.: *Responses of the Reproductive System of Hypophysectomized Rats to Injections of Pregnancy-Urine Extracts*, II. *The Female*, *Anat. Rec.* 58: 175 (Jan. 25) 1934.

27. Hamblen, E. C.: *Endocrine Gynecology*, Springfield, Ill., Charles C. Thomas, Publisher, 1939.

As has been pointed out in the preceding paragraphs, human chorionic gonadotropin does not stimulate the gametogenic elements of the mammalian ovary but does produce some of the reactions ascribed to the luteinizing hormone of the pituitary gland. In the hypophysectomized male rat the analogy is not quite so clear. In such animals, as well as in intact immature male rats, the first and constant response to the gonadotropin of human pregnancy is a hypertrophy of the interstitial cell mass of the testis, as shown by an adequate series of hypophysectomized adult male rats studied by Smith and Leonard.<sup>28</sup> Results of other workers are in good general agreement.

If the treatment of mature animals is instituted immediately after hypophysectomy, spermatogenesis as well as the size of the accessory glands can be maintained. The characteristic maintenance of the interstitial cells and the production of androgen necessary for the accessory glands are adequate. However, it has been demonstrated that androgen alone will maintain spermatogenesis in the hypophysectomized rat.<sup>29</sup> Nelson<sup>30</sup> has stated that spermatogenesis in this animal can be maintained with androgen alone if treatment is begun within ten days after hypophysectomy. In view of this finding as well as of the fact that one pronounced effect of human chorionic gonadotropin is the stimulation of the testes to produce androgen, it is impossible to be certain at present whether the maintenance of spermatogenesis by means of this gonadotropin is due to a direct action on the tubules or to an effect secondary to the stimulation of androgen production. By analogy to the female, in which the human chorionic gonadotropin certainly is not a follicle stimulator and has no gametokinetic action, one might deduce that the gametogenic effect in the male is secondary to the stimulated production of androgen. Such a deduction is supported by the fact that if a considerable period is allowed to elapse between hypophysectomy and institution of treatment, neither androgen nor chorionic gonadotropin is effective in restoring spermatogenesis, even though the latter in such a case is able to stimulate the interstitial cells quite adequately and does to a certain extent cause the tubules to enlarge. However, it has not yet been proved whether the human chorionic gonadotropin does or does not have a direct effect on the spermatogenic elements.

It must be emphasized that the rat is a rather primitive, generalized type of animal and that the foregoing observations cannot be transferred directly to man. In the instance of androgenic maintenance of spermatogenesis it is evident that the rat is a favorable species, for the observation of this maintenance reaction does not hold for the monkey<sup>31</sup> or even for the guinea pig.<sup>32</sup>

The effect of human chorionic gonadotropin on the testes of the immature monkey is primarily one of stimulating the interstitial cell growth and the produc-

tion of androgen. The tubules increase in size, but no spermatogenic effect in immature monkeys has been reported.<sup>25</sup>

Descent of the testes in monkeys accompanies the increase in androgen production following gonadotropin treatment. The therapeutic value of the gonadotropin of pregnancy urine in cryptorchidism is discussed in a subsequent chapter.

#### GONADOTROPIN OF PREGNANT MARE'S SERUM

Large quantities of a gonadotropin appear in the blood of the pregnant mare during the early stages of gestation, reaching a very high titer during the middle third of the pregnancy.<sup>25</sup> This gonadotropin, probably of chorionic origin, differs markedly from the other known gonadotropins in the respect that the physiologic responses it evokes are an interesting blend of those produced by the gonadotropic principles of human menopausal and human pregnancy urine. Very little if any of the gonadotropin is excreted in the urine of the mare. Similarly, if an extract of the gonadotropic substance is injected into laboratory animals, the gonadotropic factor is not excreted in the urine. After intravenous administration of high doses of such an extract to normal female monkeys, only traces of the gonadotropic factor appear in the urine. Its fate after injection into women is not known.

In intact immature female rats the gonadotropin of pregnant mare's serum causes follicular stimulation, followed by luteinization and marked increases in ovarian weight. It is also able to produce definite follicular stimulation in hypophysectomized rats, an action never evoked by human chorionic gonadotropin. In the hypophysectomized female rat the action of the equine gonadotropin is similar to that of the human castrate or postmenopausal principle in ability to stimulate follicular growth and, with adequate doses, to produce granulosa luteinization. However, with the equine, though not with the human, gonadotropin thecal luteinization always accompanies even slight stimulation of follicles.<sup>33</sup>

When hypophysectomized male rats are given an extract of the equine gonadotropin, the responses, interstitial hypertrophy and tubular repair, are somewhat similar to those obtained with the gonadotropic material from the urine of pregnant women.<sup>34</sup> Liu and Noble<sup>35</sup> have recently administered human and equine chorionic material to hypophysectomized adult male rats. When treatment was instituted immediately after removal of the pituitary, the equine material was able to maintain spermatogenesis and accessory gland condition so that fertile matings were obtained.<sup>34b</sup> This is in agreement with the previously discussed observations of Smith and Leonard<sup>28</sup> with human chorionic gonadotropin. In the experiments of Liu and Noble the repair of the spermatogenic elements were not completely effective if treatment was delayed, even though larger doses of the mare material were employed. In connection with these observations it is instructive to recall again the fact that in rats androgen alone will maintain but not repair the spermatogenic elements.

33. Leatham, J. H.: Responses of Hypophysectomized Immature Female Rats to Mare Serum Hormone, *Proc. Soc. Exper. Biol. & Med.* **42**: 590 (Nov.) 1939.

34. (a) Smith, P. E.: Unpublished data. (b) Evans, H. M.; Pencharz, R. I.; Simpson, M. E., and Meyer, K.: Repair of the Reproductive Mechanism in Hypophysectomized Male Rats, in Lueschner, A. O., and Teggart, F. J.: *Memoirs of the University of California, Berkeley, Calif.*, University of California Press, 1933, vol. 11, p. 301.

35. Liu, S. H., and Noble, R. L.: The Effects of Extracts of Pregnant Mare Serum and Human Pregnancy Urine on the Reproductive System of Hypophysectomized Male Rats, *J. Endocrinol.* **1**: 7 (June) 1939.

28. Smith, P. E., and Leonard, S. L.: Responses of the Reproductive System of Hypophysectomized and Normal Rats to Injections of Pregnancy-Urine Extracts; I. The Male, *Anat. Rec.* **58**: 145 (Jan. 25) 1934.

29. Walsh, E. L.; Cuyler, W. K., and McCullagh, D. R.: The Physiologic Maintenance of the Male Sex Glands: The Effect of Androgen on Hypophysectomized Rats, *Am. J. Physiol.* **107**: 508 (Feb.) 1934. Nelson, W. O.: Some Factors Involved in the Control of the Gametogenic and Endocrine Functions of the Testis, in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1937, vol. 5.

30. Nelson, W. O.: Re-Initiation of Spermatogenesis in Hypophysectomized Rats, *Am. J. Physiol.* **129**: P430 (May) 1940.

31. Smith, P. E.: Comparative Effects of Hypophysectomy and Therapy on the Testes of Monkeys and Rats, in Brouha, L.: *Les hormones sexuelles*, Paris, Hermann & Cie, 1938, pt. 3, L'hypophyse.

32. Scowen, E. F.: The Effects of Androsterone and Testosterone on the Testes of Hypophysectomized Guinea Pigs, *Anat. Rec.* **70** (supp. 3): 71 (March) 1938.

Studies on maintenance and repair of the testicular function of the hypophysectomized guinea pig by the gonadotropic extract from the serum of the pregnant mare have been made by Webster and Leatham.<sup>36</sup> The results were comparable to those of Liu and Noble with the rat. Maintenance of spermatogenesis as well as hypertrophy of the interstitial cells and accessory glands were obtained if treatment was started immediately after hypophysectomy. However, if treatment was delayed, only the interstitial cells and, consequently, the accessory glands were restored. The spermatogenic elements, though showing some improvement, were only incompletely restored.

In the female monkey the gonadotropic extract from pregnant mare's serum is a potent stimulator of follicles but produces no luteinization or fibrotic changes in the thecal wall.<sup>25</sup> In this respect the equine gonadotropin resembles the gonadotropic principles of the pituitary gland and human postmenopausal urine but differs markedly from the gonadotropin in the urine of pregnant women, which, if administered alone, does not cause follicular activation in the female monkey.

In the hypophysectomized adult male monkey the effects of the gonadotropic extract from the pregnant mare's serum are not similar to the effects in rodents. Smith<sup>37</sup> has shown that after postoperative involution of the testis the extract does not restore spermatogenic function even when the doses are high and the treatment prolonged. Smith has also pointed out that the longer treatment would probably give no better restorative effects because of the formation of antibodies against the gonadotropic substance.

The action of this substance on the gonads of men and women is discussed elsewhere.

Chemical experiments with the gonadotropin in pregnant mare's serum have yielded preparations of very high potency and considerable purity. However, even the purest of these preparations for which data are available produce physiologic effects identical with those of the crude, untreated material. This finding, if taken to indicate that the gonadotropin is a single entity, is difficult to reconcile with the claim<sup>38</sup> which has been made for the separation of the material into two fractions possessing qualitatively different physiologic activities. It may be that the results described in the latter report were due to a dosage phenomenon rather than to actual separation.

Any consideration of the effects of the gonadotropic extract from the serum of the pregnant mare must take into account the nonpermeability of the kidney to this material. As has been mentioned, the equine gonadotropin does not pass through the kidney into the urine as do other gonadotropins. It is not, therefore, surprising that the extract is as effective by intraperitoneal as by subcutaneous injection and by administration of a single dose as by administration of divided doses. In fact, there is evidence<sup>39</sup> that over short intervals a single intraperitoneal or intravenous injection is even more effective than if the same amount is divided among a number of injections. Because it is not excreted, one

can presume that the gonadotropin remains in the blood stream in effective concentration, being relatively slowly inactivated or destroyed. This fact may account for some of the differences in physiologic action between this gonadotropin and its chorionic analog in the urine of pregnant women.

## Council on Pharmacy and Chemistry

### PRELIMINARY REPORT OF THE COUNCIL

THE COUNCIL HAS AUTHORIZED PUBLICATION OF THE FOLLOWING PRELIMINARY REPORT.  
PAUL NICHOLAS LEECH, Secretary.

#### GUANIDINE HYDROCHLORIDE-CALCO

A preparation of pure guanidine hydrochloride for use in the treatment of myasthenia gravis only has been presented for the consideration of the Council by the Calco Chemical Division American Cyanamid Company. Free guanidine is also known as imido-urea, occurs as a water-soluble crystalline powder, and is generally considered to have the following structural formula:  $\text{HN}=\text{C}(\text{NH}_2)_2$ .

The manufacturer recommends daily doses of from 10 to 35 mg. per kilogram based on recently published clinical observations of Minot and her co-workers.<sup>1</sup> These observers report favorable results in five cases of myasthenia gravis observed over a considerable period which were treated with prostigmine (methylsulfate or bromide) and with guanidine hydrochloride. The latter compound was administered intravenously as a 2 per cent solution in physiologic solution of sodium chloride and orally in gelatin capsules. The authors state that solutions of guanidine hydrochloride are too irritating for subcutaneous or intramuscular use. They find that persons with myasthenia gravis can take considerably larger amounts of guanidine hydrochloride continuously over a long period of time than normal persons without causing any appreciable increase in the level of guanidine in the blood or symptoms of intoxication. They are unable to explain the greater tolerance for guanidine in persons with myasthenia gravis except to offer the opinion that guanidine may be more readily stored or transformed into some other compound in this disease and to point out that the work of Wishart<sup>2</sup> suggests that at least part of ingested guanidine may be transformed to creatine in the muscles. The authors did not attempt a study of the effect of guanidine on creatine metabolism in the cases reported to confirm Wishart's observations that the injection of guanidine increases the creatine content of the muscles in animals.

Minot and her co-workers conclude that the treatment of five cases of myasthenia gravis with guanidine hydrochloride caused a marked and well sustained improvement in muscular function without the presence of undesirable symptoms. The authors find that the patients tolerated larger doses than normal persons for an indefinite period without producing hyperguanidemia. They state that gastrointestinal and other undesirable symptoms appeared when significant elevation was persistently maintained in the blood, which could be relieved by atropine but served as a warning that guanidine should be temporarily reduced or withheld. The authors also observe that treatment may be combined with prostigmine, but that more evenly sustained improvement is obtained when guanidine makes up the larger part of medication. They feel that more work is necessary before any adequate explanation can be given of the effectiveness of guanidine in restoring function to muscles in myasthenia gravis. The authors recommend an initial trial dose of not more than 10 mg. per kilogram, subsequent early dosage to be adjusted according to the needs and tolerance of the patient under continuous hospital observation and controlled by blood level determinations; excessive dosage of ambulatory cases treated in practice to be avoided by temporary withdrawal of the drug on the appearance of gastrointestinal symptoms.

36. Webster, E. C., and Leatham, J. H.: Responses of Hypophysectomized and Normal Male Guinea Pigs to Mare Serum Hormone, to be published.

37. Smith, P. E.: Presidential Address, read before the Twenty-Fourth Annual Scientific Session of the Association for the Study of Internal Secretions, New York, 1940.

38. Evans, H. M.; Korpi, K.; Simpson, M. E., and Pencharz, R. I.: Fractionation of the Gonadotropic Hormones in Pregnant Mare Serum by Means of Ammonium Sulphate, Univ. California Publ. Anat. 1: 275, 1936.

39. Pencharz, R. I.: Factors Influencing Ovarian Response of Normal and Hypophysectomized Rat to Pregnant Mare Serum, Proc. Soc. Exper. Biol. & Med. 42: 525 (Nov.) 1939. Leatham, J. H.: The Mode of Administration as an Influence on the Effectiveness of Mare Serum Hormone in Hypophysectomized Rats, to be published.

1. Minot, Ann S.; Dodd, Katharine, and Riven, S. S.: The Use of Guanidine Hydrochloride in the Treatment of Myasthenia Gravis, J. A. M. A. 113: 553 (Aug. 12) 1939.

2. Wishart, G. M.: The Effect of the Injection of Guanidine on the Creatine Content of Muscle, J. Physiol. 53: 440 (May 18) 1920.

Minot and her collaborators<sup>3</sup> previously outlined their hypothetical basis for the therapeutic trial of guanidine in myasthenia gravis on the theory that this substance increases the sensitivity of muscles which are subnormally responsive to normal amounts of acetylcholine in this disease, whereas prostigmine hinders the destruction of acetylcholine by the normally present enzyme choline esterase. In an unpublished manuscript they<sup>4</sup> have shown that the effects of prostigmine and of guanidine are entirely dissimilar in that the former in very low concentrations inactivates choline esterase, while guanidine, even in large amounts, causes no change in enzyme activity. For some unexplained reason, toxic doses of guanidine cause a slight rise in esterase activity. The authors also point out that 25 mg. per kilogram appears to be an effective but not a toxic dose of guanidine in man. Such dosage involves somewhat larger amounts than quantities previously considered toxic according to pharmacologic observations, and the reported dissimilarity between prostigmine and guanidine is interesting in view of the close resemblance in effects generally accorded these two substances by pharmacologists. Frank, Northmann and Guttman<sup>5</sup> have shown that guanidine increases the sensitivity of normal muscles to the action of acetylcholine. All of these observations should be confirmed.

The Council has thus far recognized the use of ephedrine, prostigmine bromide, prostigmine methylsulfate and aminoacetic acid in the treatment of myasthenia gravis. Previous reports in the literature concerning the treatment of this disease indicate that the relative effectiveness of these drugs varies from case to case and that accurate evaluation of their comparative efficiency is rendered more difficult by the occurrence of spontaneous remissions. Since the advent of prostigmine, however, evidence has accumulated which suggests that this drug is probably one of the most effective single remedies yet developed for the treatment of the disease. Viets and Schwab<sup>6</sup> have reported that the results of treatment obtained in forty-four patients with myasthenia gravis over a period of two and one half years indicate that prostigmine bromide taken by mouth and supplemented with ephedrine sulfate, potassium chloride and occasionally guanidine is the most efficient form of treatment for myasthenia gravis now available. Of the forty-four patients five died, five were able to reduce the intake of prostigmine and seven showed full remissions, so that prostigmine was no longer required. The authors found that aminoacetic acid proved to be of no value in seventeen cases. Orally administered guanidine increased the effect of prostigmine in eight of twenty-five cases, in four of which results were good, whereas seventeen other patients failed to respond to guanidine; guanidine carbonate was the most satisfactory compound, but the hydrochloride was about as effective. Ephedrine sulfate enhanced the effect of prostigmine in forty-one of forty-three cases and was the most useful of the various drugs tried for this purpose. These results are partly at variance with those previously obtained and further emphasize the fact that patients with myasthenia gravis vary in their response to various types of treatment.

It should be pointed out that, according to present concepts of the action of ephedrine, prostigmine and guanidine compounds in myasthenia gravis, these substances should be regarded only as symptomatic remedies until the etiology of this disease has been established. Aminoacetic acid has been shown to exert an appreciable effect on muscle creatine retention coincident with clinical improvement in certain cases of myasthenia gravis. In the absence of a clear understanding of the possible etiologic relationship of the metabolism of muscle tissue to the disease, the choice of a therapeutic agent must be dependent on the purely empirical basis of clinical improvement. At the present

time the available evidence for the value of guanidine salts alone or as an adjunct in the treatment of myasthenia gravis is not sufficient to warrant acceptance of the drug for this purpose. Not only is additional confirmatory clinical evidence necessary to establish its therapeutic value, but further experimental investigation to clarify the rationale for its use is desirable.

The Council therefore deferred further consideration of Guanidine Hydrochloride-Calco for use in the treatment of myasthenia gravis until sufficient clinical evidence to establish its value in this condition becomes available.

## NEW AND NONOFFICIAL REMEDIES

THE FOLLOWING ADDITIONAL ARTICLES HAVE BEEN ACCEPTED AS CONFORMING TO THE RULES OF THE COUNCIL ON PHARMACY AND CHEMISTRY OF THE AMERICAN MEDICAL ASSOCIATION FOR ADMISSION TO NEW AND NONOFFICIAL REMEDIES. A COPY OF THE RULES ON WHICH THE COUNCIL BASES ITS ACTION WILL BE SENT ON APPLICATION.

PAUL NICHOLAS LEECH, Secretary.

**CAFFEINE WITH SODIUM BENZOATE** (See New and Nonofficial Remedies, 1940, p. 168).

The following dosage form has been accepted:

The Drug Products Co., Inc., Long Island City, N. Y.

*Ampuls (Hyposols) Caffeine with Sodium Benzoate, N. F., 2 cc.: An aqueous solution containing in each 2 cc. caffeine with sodium benzoate—U. S. P. 0.486 Gm. (7½ grains).*

**PROCAINE HYDROCHLORIDE** (See New and Nonofficial Remedies, 1940, p. 79).

The following dosage forms have been accepted.

*Ampul Solution Procaine Hydrochloride 1%, 1 cc.: Each cubic centimeter contains procaine hydrochloride—U. S. P. 0.01 Gm. in physiologic solution of sodium chloride q. s.*

Prepared by the Wm. S. Merrell Company, Cincinnati.

*Ampul Solution Procaine Hydrochloride 1%, 10 cc.: Each 10 cc. contains procaine hydrochloride—U. S. P. 0.1 Gm. in physiologic solution of sodium chloride q. s.*

Prepared by the Wm. S. Merrell Company, Cincinnati.

*Ampul Solution Procaine Hydrochloride 2%, 1 cc.: Each cubic centimeter contains procaine hydrochloride—U. S. P. 0.02 Gm. in physiologic solution of sodium chloride q. s.*

Prepared by the Wm. S. Merrell Company, Cincinnati.

*Ampul Solution Procaine Hydrochloride 2%, 10 cc.: Each 10 cc. contains procaine hydrochloride—U. S. P. 0.2 Gm. in physiologic solution of sodium chloride q. s.*

Prepared by the Wm. S. Merrell Company, Cincinnati.

**ASCORBIC ACID** (See New and Nonofficial Remedies, 1940, p. 530).

The following dosage form has been accepted:

*Ascorbic Acid Tablets—Merrell, 25 mg.*

Prepared by the Wm. S. Merrell Company, Cincinnati.

*Tablets Ascorbic Acid, 25 Mg.*

Prepared by the National Drug Company, Philadelphia.

No U. S. patent or trademark.

**SULFAPYRIDINE** (See New and Nonofficial Remedies, 1940, p. 494).

**Sulfapyridine-Sharp & Dohme.**—A brand of sulfapyridine—N. N. R.

Manufactured by Sharp & Dohme, Inc., Philadelphia. No U. S. patent or trademark.

*Tablets Sulfapyridine-Sharp & Dohme, 0.5 Gm. (7.7 grains).*

**BUTYN SULFATE** (See New and Nonofficial Remedies, 1940, p. 67).

The following dosage form has been accepted:

*Butyn Sulfate Tablets, 25 mg.*

**THIAMIN CHLORIDE-SQUIBB** (Thiamine Hydrochloride) (See New and Nonofficial Remedies, 1940, p. 530, and THE JOURNAL, Aug. 17, 1940, p. 534).

The following additional dosage form has been accepted:

*Solution Thiamin Chloride-Squibb, 5 cc. Vial, 100 mg. per cc.: 8-hydroxyquinoline sulfate 0.0025 per cent is used as a preservative.*

**AMPULES OF CAMPHOR** (See THE JOURNAL July 27, 1940, p. 303).

The following product has been accepted:

*Ampuls (Hyposols) of Camphor in Oil N. F. 0.195 Gm. (3 Grains), 1 cc.: Each cubic centimeter contains camphor 0.195 Gm. (3 grains) in olive oil q. s.*

Manufactured by the Drug Products Co., Inc., Long Island City, N. Y.

3. Minot, Ann S.; Dodd, Katharine, and Riven, S. S.: The Response of the Myasthenic State to Guanidine Hydrochloride, *Science* 87: 348 (April 15) 1938.

4. Minot, Ann S.; Dodd, Katharine, and Riven, S. S.: A Comparison of the Actions of Prostigmine and of Guanidine on the Activity of Choline Esterase in Blood Serum, to be published.

5. Frank, E.; Northmann, M., and Guttman, E.: Ueber diatonische Kontraktion des quergestreiften Saugtiermuskels nach Ausschaltung des motorischen Nerven. IV. Die Wirkung der Guanidine, *Arch. f. d. ges. Physiol.* 201: 569, 1923.

6. Viets, H. K., and Schwab, R. S.: The Diagnosis and Treatment of Myasthenia Gravis with Special Reference to the Use of Prostigmine, *J. A. M. A.* 113: 559 (Aug. 12) 1939.

# THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

535 NORTH DEARBORN STREET - - - CHICAGO, ILL.

Cable Address - - - "Medic, Chicago" -

Subscription price - - - - Eight dollars per annum in advance

*Please send in promptly notice of change of address, giving both old and new; always state whether the change is temporary or permanent. Such notice should mention all journals received from this office. Important information regarding contributions will be found on second advertising page following reading matter.*

SATURDAY, JANUARY 4, 1941

## HEALTH OF YOUNG MEN UNDER SELECTIVE SERVICE

The first official statistics on the results of examination of young men coming before the Selective Service Boards are now available in a statement sent to the Director of Selective Service for New York City by Col. Samuel J. Kopetzky, chief of the medical division. The total number of registrants examined by 120 local boards was 1,643. Of these 1,213 were accepted for general military service and 430 were rejected or marked "fit for limited duty only." Among the causes for rejection, 26 were for underweight, 11 for overweight, 2 for deficient height; defective vision was the primary cause of 74 rejections, diseases of the heart for 66, 28 for infantile paralysis. Whereas only 6 men were rejected because of syphilis, there were 90 men who gave a positive reaction to the Wassermann test, which caused these men to be deferred until they could be reexamined. Again the leading cause of rejection was teeth—88 men were rejected because of insufficient teeth as the main cause of rejection and 20 additional had insufficient teeth as a secondary cause.

Such figures as those here cited have been widely heralded in many places as the basis for a campaign in behalf of some new method of prevention and treatment of disease in the United States. It has been urged that we are a nation of "physical weaklings" and that some sort of national health program is immediately necessary to improve our physical health. Actually, however, this sample of those rejected does not show any specific deterioration in the population. By comparison with previous records, it indicates that the general health of our nation is good. The standards of evaluation today are far more rigid than those which were utilized in 1917. The roentgen ray for determining the presence or absence of diseases of the lung and the modern technics for examining various portions of the body, laboratory methods for the detection of changes in the blood, the Wassermann test and

similar methods of study were not used in examination of recruits in World War I.

In a bulletin just issued by the Metropolitan Life Insurance Company it is pointed out that "America's youth today is more fit to serve the country than any previous generation, including the youth of the World War." A large proportion of the rejections, it is indicated, are for ailments that are minor and often remedial and, in any event, not a bar to rigorous activity in civilian life. The improvement in the physical health of our nation is shown, of course, by lower sickness and death rates affecting those in the draft ages. In 1917-1918 about 10 per cent of the draftees were rejected because of manifest tuberculosis. The mortality from that disease has declined 75 per cent in the last quarter century among men of draft ages. Among men of the ages of 21 to 35 the reduction in heart disease mortality among those holding policies in this insurance company was 40 per cent for white men and 60 per cent for the Negroes. Our knowledge of diet, our greatly increased understanding of many diseases of the glands, the improvement in child health that has taken place in the past twenty years—all this evidence indicates that from the point of view of physical fitness we are a far better nation now than we were in 1917.

The evidence here developed should not lead us, however, to the belief that we have attained an optimum in physical fitness. The twenty-eight cases of rejection because of crippling injuries resulting from infantile paralysis are a reminder of the devastation wrought among children by this disease in the New York area in 1916. Those children are now in the draft ages. An estimate by Dr. Paul A. Neal of the National Institute of Health indicates that 60 per cent of all disabilities will be due to defects of eye and ear, mechanical defects and conditions of the heart and kidneys among the 6,000,000 men who will be examined. Many of these constitute conditions which are susceptible of rehabilitation or improvement with proper medical advice, enabling these men to be fit for limited service if not for complete military service. Approximately 140,000 men will be rejected because of tuberculosis. Not every one of them can be restored to a useful life in civilian affairs, but proper treatment and proper education may do much to lessen the chance that these men may become the foci of dissemination of this disease.

The problem of rehabilitating the men who are found to be physically or mentally defective by the Selective Service Boards is one which is being given serious consideration by many different agencies. Certainly every man who is found defective should be informed of the reasons for his rejection or deferment so that he may be given an opportunity to do the utmost on his own behalf and to utilize to the utmost the services available in his own community for rehabilitation.

In a recent address, Mr. Paul V. McNutt, coordinator of all health and welfare activities affecting the national defense, said "The task of absorbing the impact of these developments is essentially one which the local community must face squarely. . . . Responsibility for working out these essentially local problems is one which can be met primarily through the efforts of local citizens, both those who are in professional activities and those who are operating on a voluntary capacity. This is work which will require careful planning, close coordination, intelligent leadership and unity." The results of the examinations made by the Selective Service Boards and the induction boards are a challenge to the medical profession, to the social scientists, the physical educators, the public health officials and all of those concerned in the United States with the physical improvement of our population. In a recent address by Pres. William J. Hutchins of Berea College, published in the current issue of *Hygeia*, this challenge was sharply stated: "The defense of our nation cannot be entrusted to a race of adult morons, whose children are spawned into the world, to die like flies. The nation's defense cannot be entrusted to men, such as fill the venereal wards of our hospitals, such as filled the venereal sections of our army camps in the Great War. No more can our nation's defense be entrusted to men whose gangs surround our saloons and pool rooms, whose sole evidence of will power is the tenacity with which their teeth hold their cigarettes."

Scientific honesty and truth demand that we look at the problem of the people's health and evaluate the available figures clearly and justly. Again and again THE JOURNAL has pointed out that from the point of view of the national health and of physical fitness the American people can place their record well up beside that of any other nation in the world. Those who argue that this record is due primarily to the superior living conditions which have long prevailed in the United States cannot discount the achievements of modern medicine or the part played by the public health movement and medical organizations in this country. We are not a nation of "physical weaklings." Among the 16,000,000 men registered under the Selective Service Act, there can be found without too intensive a combing a sufficient number for training not only this year but in the years to come. However, the greatest asset of any nation is the health of its citizens. The detection of correctable deformities and disabilities is a problem for the medical profession. The rehabilitation of those who can be benefited is again a problem which rests primarily on the medical profession. The assumption of proper responsibilities by local, county, state and national agencies, each according to the share that it must bear in our democratic system of government, is equally desirable.

## THE PHYSICIAN AND THE OFFICIAL INDUSTRIAL HYGIENE AGENCIES

A survey of activity in the field of industrial hygiene in the United States<sup>1</sup> draws attention to the increase in the number of official consulting and investigative agencies in this field. State and federal governments as well as other agencies are expanding their programs. The range of medical activity in industrial health is so widespread and frequently of such special character as to require the services of physicians in many categories of public and private employment. Physicians in industry may be classified according to whether preventive or remedial services preponderate in their ordinary activities. At one extremity is the medically trained industrial hygienist, concerned mainly with the elimination of environmental and personal factors underlying lost time in industry. At the opposite end is the private physician in general or special practice, who is most frequently called by employers or insurance organizations to treat individual cases of compensable industrial disability. The industrial physician bridges the space between these two extremes of professional approach. He applies the principles of preventive medicine and surgery in relationship to specific working conditions and also treats accidents and diseases of occupational origin in keeping with the employer's legal responsibility. Physicians in each of these classifications have indispensable functions to perform for industry. The actual share of the total preventive medical activity which industry needs and which these varying types of physicians undertake will vary widely in keeping with local requirements. In the inevitable expansion of industrial medicine the work of physicians in all these groups must greatly increase.

Medical leadership has the responsibility for developing proper orientation in industrial health. From the evidence presented in the survey by the United States Public Health Service, opportunities for constructive services are great. Since the private practitioner treats all nonoccupational causes of lost time and a majority of occupational causes as well, reductions in industrial absenteeism rest largely in his hands. He should extend his acquaintance with industrial exposures and his competence to correct them. He should report injuries and diseases promptly to the official agencies responsible for their control and he should call on them for advice and consultation whenever local facilities for such services are incomplete or absent.

Public health administrators will find it advantageous to promote a sustained interest and watchfulness on the part of individual physicians who desire to serve more competently and extensively in this field. They should underwrite the programs which medical organizations are developing with this end in view. In the absence of enough trained personnel, existing facilities for investigation of industrial health exposures provided by

1. Pub. Health Bull. 259, U. S. Public Health Service, 1940.



# MEDICAL PREPAREDNESS

*In this section of The Journal each week will appear official notices by the Committee on Medical Preparedness of the American Medical Association, announcements by the Surgeon Generals of the Army, Navy and Public Health Service, and other governmental agencies dealing with medical preparedness, and such other information and announcements as will be useful to the medical profession.*

## MEDICAL SUPPLIES FOR GREECE

The Medical and Surgical Supply Committee of America, New York, announces that its facilities have been expanded to enable shipping medical supplies and foods to the civilian population of Greece. Heretofore, the committee has concentrated its war relief efforts to aiding noncombatants in Great Britain. The committee seeks contributions in the way of medical supplies and foods and cash for the purchase of these materials. Checks may be made out to Arthur Kunzinger of the Chase National Bank, treasurer, and mailed to the committee's headquarters, 420 Lexington Avenue, New York.

## PHYSICIANS WANTED FOR CCC CAMPS

Vacancies now exist in the CCC in the Eighth Corps Area wherein the services of physicians can be utilized as camp physicians. Applicants for these positions must be graduates of class A medical schools, must be licensed to practice medicine in at least one state and must be physically qualified. Applications should be addressed to The Surgeon, CCC, Eighth Corps Area, Fort Sam Houston, Texas.

If selected, physicians must report to their first duty station at their own expense and, on being relieved from duty, return transportation must also be at the expense of the individual. They will be required to furnish necessary medical treatment to the personnel of CCC camps and in addition will be required to perform such other duties as may be directed by their superior officers.

## RADON PRODUCTION PLANT GIVEN TO ENGLAND

Radiologists in England have been forced by German bombers to abandon most of their clinical work with radium owing to the danger of losing radium, although research is going ahead in other branches of medicine and physics despite the war. The British War Relief Society in New York City, at the urgent request of the British Hospitals Association, has cabled \$25,000 to London to establish a subterranean plant for the production of radon, an emanation product of radium that can be effectively used as a substitute. This American sponsored radon unit will provide radium treatment for the 50 per cent of cancer patients in Great Britain who have been unable to have that aid since the Germans began bombing Great Britain. The head of the British War Relief Society, Mr. Winthrop W. Aldrich, chairman of the board of the Chase National Bank, said that the radon bank will be set up far from the reach of bombs and would be under the direction of Prof. Sidney Russ, chief of the department of biophysics at the Middlesex Hospital Medical School. Professor Russ already has one small radon plant in operation which supplies half of England. Radon is a gas given off by radium and is as powerful as radium itself for a few days, according to Gioacchino Failla, physicist at the Memorial Hospital in New York, and it can be used in the same way as radium. After a few days, however, the radon tubes lose their effectiveness and become then completely harmless should they be lost. Radon was discovered simultaneously by Mme. Curie in France and by Sir Ernest Rutherford in England and was first used in 1913 in the treatment of cancer.

## ARMY RESERVE OFFICERS ORDERED TO ACTIVE DUTY SECOND CORPS AREA

The following additional medical reserve corps officers had been ordered to active duty by the Commanding General, Second Corps Area, up to December 20. The Second Corps Area comprises the states of New York, New Jersey and Delaware.

AMATO, Louis L., 1st Lieut., New York, 2d Military Area.  
CANDILORO, Carl G., Captain, New York, 2d Military Area.

## THIRD CORPS AREA

The following additional medical reserve corps officers had been ordered to extended active duty by the Commanding General, Third Corps Area, up to December 13. The Third Corps Area comprises the states of Pennsylvania, Virginia, District of Columbia and Maryland.

D'ARTA, Edward J., 1st Lieut., Brooklyn, 2d Military Area.  
EICHNER, Daniel H., Captain, New York, 2d Military Area.  
KWIAT, Joseph A., 1st Lieut., North Plainfield, N. J., 3d Military Area.  
LIPTON, Harold, Captain, Brooklyn, 2d Military Area.  
MOORE, Joseph M., Captain, New York, 2d Military Area.  
NADLER, Julius, 1st Lieut., Brooklyn, 2d Military Area.  
REID, Charles D., Captain, Syracuse, N. Y., 1st Military Area.  
SHAPIRO, Benjamin, 1st Lieut., Jackson Heights, N. Y., 2d Military Area.  
SHEERAN, James D., 1st Lieut., Brooklyn, 2d Military Area.

CIACCIA, Nicholas Louis, 1st Lieut., Pittsburgh.  
COPE, Fredrick Trevor, 1st Lieut., Philadelphia.  
FITZPATRICK, James Joseph, 1st Lieut., Pittston, Pa.  
FRIEDMAN, Joseph Marshall, 1st Lieut., Washington, D. C.  
FUGITT, Elmer Wink, Captain, Washington, D. C.  
GOLDMAN, Sidney Saunders, Major, Philadelphia.  
MARYANOV, Lawrence, 1st Lieut., Vienna, Md.  
POTTER, Richard Clute, Jr., 1st Lieut., Marion, Va.  
STEINBERG, Morris William, 1st Lieut., Baltimore.

## FOURTH CORPS AREA

The following additional medical reserve corps officers have been ordered to active duty by the Commanding General, Fourth Corps Area, since Dec. 13, 1940. The Fourth Corps Area comprises the states of Tennessee,

North Carolina, South Carolina, Alabama, Georgia, Mississippi, Florida and Louisiana.

ADAMO, Frank S., Lieut. Col., Tampa, Fla.  
ALEXANDER, Lassar, 1st Lieut., Miami, Fla.

ANNIS, Jere W., 1st Lieut., Lakeland, Fla.  
BUCHNER, Edward F., 1st Lieut., Chattanooga, Tenn.  
CANIPPELLI, Edward, 1st Lieut., Jacksonville, Fla.  
CANIZARO, Vito J., 1st Lieut., Vicksburg, Miss.  
CLACK, John M., 1st Lieut., West Point, Ga.  
CUTTINO, John T., 1st Lieut., Columbia, S. C.  
DURST, George G., 1st Lieut., Greenwood, S. C.  
ESSRIG, Irving M., 1st Lieut., Tampa, Fla.  
FAULKNER, Roscoe, 1st Lieut., Trenton, Tenn.  
FOWLER, Shelton F., 1st Lieut., Nashville, Tenn.  
GARY, Robert E., 1st Lieut., Tusculumbia, Ala.  
GRIFFIN, James C., 1st Lieut., Tampa, Fla.  
GRIZZARD, Thomas, 1st Lieut., Goodlettsville, Tenn.  
HAINES, Charles E., Jr., 1st Lieut., Durham, N. C.  
HULL, Joseph A., 1st Lieut., DeKalb, Miss.  
INGLE, Charles W., Jr., 1st Lieut., Memphis, Tenn.  
KEELS, Lucius B., 1st Lieut., Bishopville, S. C.  
KAPLAN, Saul H., 1st Lieut., Miami Beach, Fla.  
KING, Joseph H., 1st Lieut., Summerton, S. C.  
LEFHOLZ, Rothwell, 1st Lieut., Coral Gables, Fla.  
LESTER, Roy T., 1st Lieut., Coughatta, La.  
McLANE, Francis C., 1st Lieut., Abbeville, S. C.  
McRAE, Cameron F., Jr., 1st Lieut., Mars Hill, N. C.  
MARTIN, Benjamin F., 1st Lieut., Winston-Salem, N. C.

OVERTON, Fred W. T., Captain, Nashville, Tenn.  
POOLE, Harold L., 1st Lieut., Spartanburg, S. C.  
POWELL, Cuthbert E., 1st Lieut., Swainsboro, Ga.  
SHELTON, George W., 1st Lieut., Manchester, Tenn.  
STARZYNSKI, Florian B., Captain, Birmingham, Ala.  
TEASLEY, Gerald H., 1st Lieut., Athens, Ala.  
TREHERNE, Alfred J., Captain, Atmore, Ala.  
WHITMAN, Oscar F., 1st Lieut., Statesboro, Ga.  
WORLEY, Wyeth B., 1st Lieut., Shreveport, La.

#### Relieved from Duty

The following officers previously reported have been relieved from duty or their orders have been revoked:

CHAMBERS, Wallace L., 1st Lieut., Pickens, Miss.  
EDELSON, Edmond K., 1st Lieut., New Orleans.  
HAY, Floyd B., 1st Lieut., Byrdstown, Tenn.  
MARTIN, Carl T., 1st Lieut., Haleyville, Ala.  
SCOTT, Wood H., 1st Lieut., Bonita, La.  
SLIPAKOFF, Leon, 1st Lieut., New Iberia, La.  
SORRELLS, John E., 1st Lieut., Iowa, La.  
STOVALL, James T., Jr., 1st Lieut., Jefferson, Ga.  
YOUNG, Henry D., Jr., 1st Lieut., Bushnell, Fla.

### SIXTH CORPS AREA

The following additional medical reserve corps officers had been ordered to extended active duty by the Commanding General, Sixth Corps Area, up to December 20. The Sixth Corps Area comprises the states of Wisconsin, Illinois and Michigan.

APPELMAN, Howard B., Captain, Detroit.  
BASS, Howard H., Captain, Chicago.  
BROWNSTEIN, Stanley, 1st Lieut., Chicago.  
CONN, Harold, 1st Lieut., Detroit.  
DeGROAT, Albert, Captain, Detroit.  
DeSALVO, Michael F., 1st Lieut., Madison, Wis.  
DOKTORSKY, Abraham, 1st Lieut., Chicago.  
FELDMAN, Nathaniel LeR., Captain, Detroit.  
GOLDBERG, Aaron L., 1st Lieut., Chicago.  
GUTMAN, Emil, 1st Lieut., Chicago.  
KOBIRIN, Meyer W., 1st Lieut., Gary, Ind.  
LEVENSON, Joseph M., 1st Lieut., Chicago.  
LINK, Gustave S., 1st Lieut., Chicago.

NEAL, Lovell A., 1st Lieut., Mattoon, Ill.  
MARCHMONT, Robinson Harry, 1st Lieut., Chicago.  
MILLARD, Allen LaM., Major, Marshallfield, Wis.  
OLWIN, John H., 1st Lieut., Chicago.  
OWEN, Clarence I., Major, Detroit.  
PALMER, Algernon A., Captain, Chelsea, Mich.  
PEARLMAN, Maurice D., 1st Lieut., Chicago.  
ROMANSKI, Arthur F. S., 1st Lieut., Berwyn, Ill.  
ROSEN, Irving Isadore, 1st Lieut., L'Anse, Mich.  
ROSENBLOOM, Harold H., Captain, Chicago.  
ROSENGARD, Jerome L., Captain, Chicago.  
SASS, Louis A., 1st Lieut., Chicago.  
SINTZEL, Alois R., Captain, Belleville, Ill.  
STAFFORD, Wilfred F., 1st Lieut., Mattoon, Ill.  
STANLEY, Arthur LaG., 1st Lieut., Pontiac, Mich.  
STARSIK, Casimir R., 1st Lieut., Chicago.  
STOLL, John E., Major, Chicago.  
SURRELL, Matthew A., 1st Lieut., Newberry, Mich.  
SWIFT, Frederick J., 1st Lieut., Chicago.  
THEIS, Edward H., Major, Granite City, Ill.  
WALKER, Enos G., Major, Detroit.

### SEVENTH CORPS AREA

The following additional medical reserve corps officers had been ordered to active duty by the Commanding General, Seventh Corps Area, up to December 20. The Seventh Corps Area comprises the states of North Dakota, South Dakota, Minnesota, Nebraska, Iowa, Kansas, Missouri, Arkansas and Wyoming.

ANDRE, Gaylord Ross, 1st Lieut., Lisbon, Iowa, Fort Sam Houston, Texas.  
DWORAK, Arthur Francis, Captain, St. Paul, Fort Bliss, Texas.  
EVERITT, Neill Jay, Lieut. Col., Omaha, Surgeon's Office of Seventh Corps Area, Omaha.  
KRANSON, Seymour Julian, Captain, Independence, Mo., Fort Bliss, Texas.

### NINTH CORPS AREA

The following additional medical reserve officers had been ordered to extended active duty by Ninth Corps Area order up to December 14:

ADAMS, Elliott L., 1st Lieut., Lodi, Calif., Presidio of Monterey and Fort Ord, Calif.  
ARNOWITZ, Isaac, 1st Lieut., San Francisco, Fort Scott, San Francisco.  
BARTLETT, John C., 1st Lieut., Berkeley, Calif., Presidio of San Francisco, Calif.  
BODE, Arnold G. H., 1st Lieut., Sierra Madre, Calif., Presidio of Monterey and Fort Ord, Calif.  
BUSH, George, 1st Lieut., Long Beach, Calif., Fort MacArthur, Calif.  
CANNING, Thomas E., 1st Lieut., Colville, Wash., Fort Lewis, Wash.  
CARLLE, Thomas B., 1st Lieut., Seattle, Fort Lewis, Wash.  
CHAMPOUX, Clement G., 1st Lieut., Selah, Wash., Camp Clatsop, Ore.  
COFFELT, Ralph W., 1st Lieut., Los Angeles, Presidio of Monterey and Fort Ord, Calif.  
CRONIN, Daniel J., 1st Lieut., San Francisco, Presidio of San Francisco, Calif.  
DEBUSK, Fred G., 1st Lieut., Visalia, Calif., Camp McQuaide, Calif.

DEMPSEY, Thomas F., 1st Lieut., San Bernardino, Calif., Presidio of San Francisco, Calif.  
FOWLER, John D., 1st Lieut., Los Angeles, Fort MacArthur, Calif.  
GOLD, Rubin L., 1st Lieut., San Francisco, Presidio of Monterey and Fort Ord, Calif.  
KRIEGER, Sherburne, 1st Lieut., Los Angeles, Camp McQuaide, Calif.  
LANDERS, Clyde H., 1st Lieut., Altadena, Calif., Presidio of Monterey and Fort Ord, Calif.  
LAWTON, Latham B., Captain, Jackson, Wyo., Fort F. E. Warren, Wyo.  
MAXIMOV, Nicholas G., 1st Lieut., San Francisco, Presidio of Monterey and Fort Ord, Calif.  
OWENS, Raymond W., 1st Lieut., Oildale, Calif., Camp McQuaide, Calif.  
PARROTT, Robert M., 1st Lieut., Tacoma, Wash., Fort Lewis, Wash.  
SPISHAKOFF, Nathan M., 1st Lieut., Los Angeles, 41st Division, Camp Murray, Wash.  
UNSELL, Ira M., 1st Lieut., Santa Monica, Calif., 29th Engineer Battalion, Portland, Ore.  
ZIDE, Harry A., 1st Lieut., Los Angeles, Presidio of Monterey and Fort Ord, Calif.

### NEW NAVY MEDICAL OFFICERS

The following physicians are reported to have qualified by examination for appointment in the Medical Corps of the U. S. Navy and were commissioned assistant surgeons with rank of lieutenant (junior grade), October 2:

BLALOCK, Tully T., Charleston, S. C.  
BROWN, Walter E., Rocky Mountain, N. C.  
CHASTEN, Stephen M., Stoughton, Wis.  
CUNNINGHAM, John J., Pensacola, Fla.  
DRUCKEMILLER, William H., New York.  
FUELLING, James L., Newburgh, Ind.

GIOTTA, Peter J., Bronx, New York.  
JANUS, William L., Philadelphia.  
KANE, John J., Beaufort, S. C.  
KELLER, John H., M. C., China Grove, N. C.  
KULIESIS, Adolph P., Mattapan, Mass.  
MACKOSE, William F., Beaver Dam, Wis.  
MARKOWITZ, Herbert A., Washington, D. C.  
MILLER, Myles R., Kennett Square, Pa.  
MOLLING, Grant F., Smithfield, N. C.  
RENAUD, Oliver V., Brooklyn.  
SIESS, Eugene E., Los Angeles.  
SNOWDEN, William M., Philadelphia.  
STONE, Evan C., Jr., Minot, N. D.  
WRIGHT, Donovan G., Oak Park, Ill.



# ORGANIZATION SECTION

## OFFICIAL NOTES

### RADIO BROADCASTS

"Doctors at Work" is the title of the sixth annual series of dramatized radio programs being presented by the American Medical Association and the National Broadcasting Company.

The series opened Wednesday, Nov. 13, 1940, and will run for thirty consecutive weeks, closing with a broadcast from the A. M. A. meeting at Cleveland on June 4. The program is scheduled for 10:30 p. m. eastern standard time (9:30 central, 8:30 mountain, 7:30 Pacific time) over the Blue network, other N. B. C. stations and Canadian stations.

The programs are broadcast on what is known in radio as a sustaining basis; that is, the time is furnished gratis by the radio network and local stations, and no revenue is derived from the programs. Therefore, local stations may or may not take the programs, at their discretion, except those stations which are owned and operated by the National Broadcasting Company.

Some radio stations may be unable to broadcast the program at the regular scheduled time and may transcribe and broadcast it at another hour or even on another day. It is advisable therefore to verify the time by reference to local newspapers or by telephoning the local Blue network stations.

The programs will dramatize what modern medicine offers the individual in the way of opportunities for better health and the more successful treatment of disease. Incidental to this main theme the programs will explain the characteristics of the different fields of modern medicine and its specialties.

Descriptive posters for local distribution may be had gratis from the Bureau of Health Education, American Medical Association, 535 North Dearborn Street, Chicago. Program titles will be announced weekly in *THE JOURNAL* and monthly in *Hygeia*, The Health Magazine.

Tickets are available for each broadcast. Address the Bureau of Health Education, American Medical Association, 535 North Dearborn Street, Chicago. Tickets are free, but a stamped self-addressed envelop should accompany requests.

The next three programs to be broadcast, together with their dates and their titles, are as follows:

January 8. Your Eyes.  
January 15. Best Foot Forward.  
January 22. Blocking Pain.

Mail received from radio listeners to "Doctors at Work" has indicated a wide acceptance of the program as an interesting entertainment feature as well as a source of information. Letters received represent many shades of opinion, including those of physicians, teachers, clergymen, mothers and business men.

### ADDRESSES BY OFFICIAL STAFF

DR. PAUL C. BARTON:

Jan. 20—Woman's Auxiliary to the North Side Branch of the Chicago Medical Society, Chicago.

DR. W. W. BAUER:

Jan. 6—Chicago Medical Society, Woman's Auxiliary, North Shore Branch, Chicago.

Jan. 6—Elgin Lions Club, Elgin, Ill.

Jan. 9—Pennsylvania Health Institute, Harrisburg.

Jan. 13—High School, Manitowoc, Wis.

Jan. 13—Manitowoc County Medical Society, Woman's Auxiliary, Manitowoc, Wis.

Jan. 13—Rotary Club, Manitowoc, Wis.

Jan. 16—Atwood Heights Parent Teacher Association, Blue Island, Ill.

Jan. 18—American Association of University Women, Elgin, Ill.

DR. MORRIS FISHER:

Jan. 10—Commonwealth Fund, New York.

Jan. 14—Chicago Philanthropic Club, Chicago.

Jan. 15—Indiana Livestock Breeders' Association, Lafayette, Ind.

Jan. 29—Chicago Woman's Club, Chicago.

DR. FRANK H. LAHEY:

Jan. 11—Connecticut State Medical Society, New Haven, Conn.

Jan. 13—Johns Hopkins Medical Society, Baltimore.

Jan. 17—Newton Center Men's Club, Newton Center, Mass.

Jan. 30—Lackawanna County Medical Society, Scranton, Pa.

DR. CARL M. PETERSON:

Jan. 18—Secretaries' Conference of the West Virginia State Medical Association, Charleston.

DR. PAUL A. TESCHNER:

Jan. 10—Chicago Boys Club, Chicago.

Jan. 14—Lake View Woman's Club, Chicago.

Jan. 24—Cook County Federation of Women's Clubs, Chicago.

DR. NATHAN B. VAN ETEN:

Jan. 10—Pennsylvania Health Institute, Harrisburg.

Jan. 10—Lycoming County Medical Society, Williamsport, Pa.

Jan. 21—Junior League, New York.

Jan. 28—Woman's Auxiliary, Nassau County Medical Society, Garden City, N. Y.

## WOMAN'S AUXILIARY

### Oregon

The annual Health Education Day program and tea sponsored by the auxiliary to the Multnomah County Medical Society was held October 28. Dr. George E. Henton, one of the councillors for the Oregon State Medical Society, spoke on "The Program of the Oregon State Medical Society to Provide Care for the Low Wage Group." Members of all outstanding women's organizations in the city were issued a general invitation by letter to their respective presidents. This was followed by a personal printed invitation to individual members. Auxiliary members were asked to be responsible for one guest. The auxiliary held a combined November and December meeting in the Medical Dental Building Auditorium on November 25. After the regular business meeting Miss Nell A. Unger, head librarian of the Library Association of Portland, spoke on "Reading for Pleasure."

### Wisconsin

The Milwaukee County auxiliary, Mrs. C. D. Partridge, president, met October 11 in Milwaukee. Mrs. William Liefert reported on the Red Cross work done during the summer and Mrs. Gerald H. Friedman, state chairman of Hygeia, presented the state program for 1940-1941. Two interesting speakers featured the November meeting of the auxiliary. Dr. Ralph P. Sproule, president of the state medical society, talked on "Social Problems Confronting the Medical Profession." "Axis Bid for Africa" was the subject of the talk by Dr. Howard J. McMurray, professor of political science at the University of Wisconsin Extension Division. At the November meeting of Milwaukee County's study group, Mrs. Edgar Behnke gave a paper on an eastern medical plan. Mrs. Ervin Hansher led the study group.

## Medical News

(PHYSICIANS WILL CONFER A FAVOR BY SENDING FOR THIS DEPARTMENT ITEMS OF NEWS OF MORE OR LESS GENERAL INTEREST: SUCH AS RELATE TO SOCIETY ACTIVITIES, NEW HOSPITALS, EDUCATION AND PUBLIC HEALTH.)

### CONNECTICUT

**Changes in Health Officers.**—The *Connecticut Health Bulletin* announces the following appointments of health officers:

Dr. Joseph Bruce Crook, of East Haddam.  
Dr. John S. Staneslow, of Prospect.  
Dr. Andrew O. Laakso, of Killingly, succeeding Dr. George S. Lambert.  
Dr. Martin L. O'Neill, Jewett City, of Voluntown, succeeding Dr. John H. McLaughlin, Jewett City.  
Dr. Oscar Rogol, of Oxford.

**Course on Diseases of Nutrition.**—The Clinical Congress of the Connecticut State Medical Society will open a postgraduate course on the diseases of nutrition at Yale University School of Medicine, New Haven, January 9, to continue each Thursday for fourteen weeks. Subjects covered in the course include:

The Nature and Functions of Dietary Constituents.  
Carbohydrate Interrelationships.  
Protein and Fat Deficiencies.  
General Characteristics and Properties of Vitamins—The Problem in Man.  
Water, Sodium, Iodine, Potassium and Magnesium in Health and Disease.  
Calcium, Phosphorus and Vitamin D.  
Vitamin B Deficiency.  
Vitamin A, C, K (P).  
Iron and Hemopoietic Factors.  
Pathology of Dietary Deficiencies.  
The Calculation of Diets.

### DISTRICT OF COLUMBIA

**Postgraduate Course in Ophthalmology.**—A preliminary announcement has been received concerning a postgraduate course in ophthalmology to be given at the George Washington University School of Medicine, Washington, April 7-12. Guest lecturers will include:

Dr. James H. Allen, Iowa City, Treatment of the Staphylococcal Infections of the Eye with Special Reference to Immunotherapy.  
Dr. Arthur J. Bedell, Albany, N. Y., Diseases of the Fundus Oculi.  
Dr. Francis Bruce Fracliek, Ann Arbor, Mich., Anatomy of the Eye.  
Dr. LeGrand H. Hardy, New York, Orthoptic Training.  
Dr. Parker Heath, Detroit, Ocular Therapeutics.  
Dr. Peter C. Kronfeld, Chicago, Ocular Tuberculosis.  
Dr. Angus L. MacLean, Baltimore, Reading Disabilities.  
Dr. James I. Moore, Baltimore, Use of X-Rays and Radium in Ophthalmology.  
Dr. Joseph Earle Moore, Baltimore, Ocular Syphilis.  
Dr. Algernon B. Reese, New York, Glaucoma.  
Dr. Bernard Samuels, New York, Pathology of the Eye.  
Dr. Theodore L. Terry, Boston, Cataract Surgery.  
Dr. James Watson White, New York, Disturbances of Ocular Motility.

A symposium on refraction will be a feature of the course with Drs. Walter B. Lancaster, Hanover, N. H., Allen Greenwood, Boston, and Sylvester Judd Beach, Portland, Maine, as the speakers. Members of the staff of the department of ophthalmology of the university who will participate in the course will include:

Dr. William Thornwall Davis, Headache.  
Dr. Ernest A. W. Sheppard, Ophthalmic Lenses.  
Dr. G. Victor Simpson, Telescopic and Contact Lenses.  
Dr. Edgar Leonard Goodman, Preparation of Material for Animal Surgery.  
Dr. Ronald A. Cox, Physiology and Disease of the Lacrimal Apparatus.

### FLORIDA

**Personal.**—Dr. Carroll T. Bowen, Jacksonville, director of venereal disease control for the Duval County health unit, has been appointed director of the Broward County health unit, with headquarters in Fort Lauderdale.—Dr. Erwin F. Hoffman, Detroit, has been appointed health officer of Hendry County, succeeding Dr. Charles W. Pease, who was transferred to Jacksonville.—Dr. Walter L. Shackelford, for thirteen years superintendent of the Good Samaritan Hospital, West Palm Beach, has resigned to enter private practice.

### ILLINOIS

**Typhoid Traced to Carrier.**—A woman typhoid carrier was believed to be the source of an outbreak of typhoid in the Pleasant Hill School in Tazewell County in October, involving ten school children. All the patients had eaten luncheon served at the school. An examination of fecal specimens from the six persons who had worked in connection with the luncheon service showed typhoid bacilli in the specimen taken

from one woman. This woman gave a history of typhoid in 1916. She was removed from work as a food handler, and all the pupils, other than those ill, were vaccinated against typhoid. It was recommended that all other contacts of the patients be vaccinated also.

### Chicago

**Daily News Appoints Science Editor.**—Mr. James C. Leary, who has been specializing in science writing on the staff of the *Chicago Daily News* for the past several years, has been named science editor of that paper.

**Branch Meetings.**—Dr. Grover C. Penberthy, Detroit, addressed the Jackson Park Branch of the Chicago Medical Society, December 19, on "Treatment of Burns."—Dr. Walter C. Alvarez, Rochester, Minn., discussed "Abdominal Pain" before the Calumet Branch, December 20.

**Dr. Phemister Named to New Professorship.**—Dr. Dallas B. Phemister, professor of surgery and chairman of the department, University of Chicago School of Medicine, has been designated the first holder of the newly created Thomas D. Jones professorship. The new chair was recently established to honor the late Thomas Davies Jones, pioneer Chicago attorney and industrialist, who died in 1930. Mr. Jones had been a major benefactor of the University of Chicago, its medical school and the Frank Billings Medical Clinic. Born in Carbondale, Ill., in 1882, Dr. Phemister received his degree in medicine in 1904 from Rush Medical College. He has been a member of the staff of the University of Chicago since 1925 and is a past president of the American Surgical Association and of the Society of Clinical Surgery.

### MICHIGAN

**Personal.**—Dr. George Louis LeFevre, Muskegon, was honored recently when the Muskegon County Medical Society *Bulletin* was dedicated to him. Dr. LeFevre was president of the county medical society in 1905 and again in 1922 and has been medicolegal adviser of the society since 1915. In 1920 he was elected to the council of the Michigan State Medical Society, serving his district until his election as president of the state society in 1933.—The Tuscola County Medical Society and local residents recently honored Dr. George Bates, Kingston, with a reception to observe his completion of fifty years in the practice of medicine.

**Annual Battle Creek Conference.**—The annual Battle Creek Medical Conference was held at the Battle Creek Sanitarium, December 3. It is sponsored by the Calhoun County Medical Society, the sanitarium, the Battle Creek Academy of Medicine and Dentistry, and the combined staffs of Leila Post Montgomery, American Legion and Community hospitals. Included among the out of state speakers were:

Dr. James Roscoe Miller, The Treatment of Cardiac Decompensation.  
Dr. Cleveland J. White, Treatment of Common Skin Diseases.  
Dr. David E. Markson, Newer Developments in the Medical Treatment of Arthritis.  
Dr. James K. Stock, Surgical Treatment of Arthritis.  
Dr. Michael L. Mason, The Immediate Care of Raw Surfaces.  
Dr. Arthur E. Mable, Gastroenterology in General Practice.

All are on the staff of Northwestern University Medical School, Chicago. Dr. Morris Fishbein, editor of *THE JOURNAL*, Chicago, gave an address at the banquet.

### MINNESOTA

**Dr. Ivy to Deliver Judd Lecture.**—Dr. Andrew C. Ivy, Nathan Smith Davis professor of physiology and head of the department of physiology and pharmacology at Northwestern University Medical School, Chicago, will deliver the eighth E. Starr Judd Lecture at the University of Minnesota in the Medical Science Amphitheater, January 15. His subject will be "The Mechanisms of Gastric Secretion." The late Dr. Edward Starr Judd, an alumnus of the Minnesota medical school, established this annual lectureship in surgery a few years before his death.

**Supreme Court Refuses Review of Suspension of Homeopath's License.**—The Supreme Court of the United States announced its refusal, November 12, to review the case in which the Minnesota State Board of Medical Examiners had suspended for five years the license of Dr. Gottfried Schmidt, Lake City. Dr. Schmidt's license was suspended Dec. 16, 1938 following a hearing before the board when it was charged that he was guilty of immoral, dishonorable and unprofessional conduct as defined by law. It was disclosed that Dr. Schmidt had attempted to diagnose cancer, ulcers and other serious conditions by the use of a piece of wood pulp

paper moistened with the patient's saliva. The moistened paper was placed on the abdomen of either the patient or a woman subject employed by Dr. Schmidt in his office at Lake City. He also claimed that he had a machine with which he could broadcast treatments to absent patients. Following the suspension of his license, Dr. Schmidt appealed to the District Court of Ramsey County. After a hearing before Judge Carlton F. McNally, the court affirmed the action of the medical board, holding that the board's action "was neither arbitrary, oppressive nor unreasonable." Dr. Schmidt then appealed to the Supreme Court of Minnesota, which court, May 17, handed down a unanimous opinion written by Justice Royal A. Stone affirming the District Court of Ramsey County. Then Dr. Schmidt served notice of appeal to the Supreme Court of the United States. Dr. Schmidt was born in Minnesota in 1871 and graduated at the University of Minnesota College of Homeopathic Medicine and Surgery, Minneapolis, in 1903.

### MISSOURI

**Sauer to Be Deported.**—Rudy H. Sauer, "a practical male nurse," was recently sentenced to imprisonment for a year and a day for violation of the Harrison Narcotic Law and will be deported to Canada. On November 7 Sauer was found by police and narcotic agents in St. Louis in illegal possession of narcotics. A federal warrant charging violation of the narcotic laws was issued against Sauer November 10. It was alleged that he entered "medical practice" and affixed the title "Dr." to his calling card after receiving a physician's medical kit from a friend. Sauer was arrested after he had inserted an advertisement in two afternoon newspapers in St. Louis for a girl "of pleasing personality to assist a doctor." The mother of a girl interviewed asked the police to question "Dr." Sauer. The police reported finding narcotic tablets in the kit. Sauer is said to have admitted later that he had administered narcotics to a man as a treatment for insomnia.

### NEW JERSEY

**Nweeya Poses as Medical Missionary.**—A New Jersey physician reports a fraud in which the swindler posed as a medical missionary, selling a book he had written on his experiences in Persia. The man said that his name was Samuel K. Nweeya, that he was a graduate of the University of Pennsylvania and that he was a friend of various physicians in New Jersey. He displayed a list of subscriptions containing seventy or more names of prominent physicians in and near Newark. His story was that he had been forced to return to the United States because of his wife's health and that he was selling the book to obtain funds for her treatment. One physician gave him a check for \$3, which was endorsed with a nonexistent address.

### NEW YORK

**Survey of Mental Hospitals.**—Governor Lehman has appointed an unofficial commission to make a survey of ways and means of reducing admissions to and the population of state mental institutions. Homer Folks, secretary of the State Charities Aid Association, is chairman of the commission and others invited to serve are:

Dr. Karl M. Bowman, director, psychiatric division, Bellevue Hospital, and professor of psychiatry, New York University College of Medicine, New York.

Dr. Clarence O. Cheney, medical director, New York Hospital, Westchester Division, White Plains.

Miss Hester B. Crutcher, director of psychiatric social work, state department of mental hygiene, Albany.

Stanley P. Davies, executive director, Community Service Society of New York.

Dr. William J. Tiffany, Albany, state commissioner of mental hygiene, Albany.

Dr. Lawrence Kolb, assistant surgeon general, U. S. Public Health Service, Washington, D. C.

Dr. Frederick W. Parsons, former state commissioner of mental hygiene, New York.

Dr. William L. Russell, consulting psychiatrist, Payne Whitney Psychiatric Clinic, New York.

Dr. Nolan D. C. Lewis, director, New York State Psychiatric Institute and Hospital, and professor of psychiatry, Columbia University College of Physicians and Surgeons, New York.

Dr. George S. Stevenson, medical director, National Committee for Mental Hygiene, New York.

### New York City

**The Janeway Lecture.**—Dr. Irvine H. Page, director of the Lilly Laboratory for Clinical Research, Indianapolis, will deliver the Edward Gamaliel Janeway Lecture at Mount Sinai Hospital, January 10, on "The Nature of Experimental and Clinical Hypertension."

**Professor of Orthopedic Surgery Appointed.**—Dr. Alan DeForest Smith, clinical professor of orthopedic surgery at Columbia University College of Physicians and Surgeons, has been appointed professor. He succeeds Dr. Benjamin P. Farrell, who retired June 30. Dr. Smith also succeeded Dr. Farrell as surgeon in chief of the New York Orthopedic Dispensary and Hospital.

**Annual Medical-Dental Meeting.**—The annual combined meeting of the first and second district dental societies and the five county medical societies of New York was held at the Hotel Pennsylvania, December 2. A symposium on focal infection was presented at the morning session by Drs. William B. Rawls and Samuel Weiss, New York, and Joseph L. T. Appleton, D.D.S., Philadelphia. In the afternoon a symposium on acute infections of the face and neck was presented by Dr. Oscar V. Batson, Philadelphia, Dr. Charles Gordon Heyd and Malcolm Wallace Carr, D.D.S.

**Instruction in Obstetrics.**—The New York Academy of Medicine will present a series of lectures in obstetrics for practitioners beginning January 8 with an address by Dr. Charles A. Gordon, Brooklyn, on "Immediate Treatment of Hemorrhage." Subsequent lectures will be:

January 15, Dr. Arthur J. Murphy, Urinary Tract Complications in Pregnancy, Labor and the Puerperium.

January 22, Dr. Herman O. Mosenthal, Diabetes in Pregnancy.

January 29, Dr. Nicholson J. Eastman, Baltimore, Asphyxia in the Newborn.

February 5, Dr. Philip F. Williams, Philadelphia, Metabolism in Pregnancy, Including Vitamin Deficiency.

**Meeting of Chest Physicians.**—The New York State chapter of the American College of Chest Physicians will hold a session at the Hotel Biltmore, January 17, with the following speakers:

Dr. Chevalier L. Jackson, Philadelphia, Bronchoscopy in Diseases of the Chest.

Dr. Wilbur Emory Burnett, Philadelphia, Surgery of Carcinoma of the Lung.

Dr. Leonard Greenburg, state department of labor, Industrial Pulmonary Diseases.

Dr. Edgar Mayer, Tuberculosis in the Army Under Present Epidemiologic Conditions.

Dr. Arthur Q. Penta, Schenectady, Postoperative Atelectasis: Diagnosis, Prevention and Treatment.

Dr. James S. Edlin, Artificial Pneumothorax in the Treatment of Pulmonary Tuberculosis.

**Anatomy Department Honors Former Professor.**—The department of anatomy of New York Medical College, Flower and Fifth Avenue hospitals was formally designated the "William Waldo Blackman Laboratory of Anatomy" at a ceremony, November 19. Conrad E. Tharaldsen, Ph.D., professor of anatomy, presided at the meeting and William K. Gregory, Ph.D., professor of vertebrate paleontology, Columbia University, and curator of the department of comparative anatomy at the American Museum of Natural History, made the principal address, on "Evolutional Causes of the Misery of Mankind." Dr. Blackman is an alumnus, former professor of anatomy and president of the college alumni association and is now vice chairman of the board of trustees.

### OREGON

**Society News.**—A symposium on shock was presented at the meeting of the Multnomah County Medical Society, Portland, November 20, by Drs. Aubrey M. Davis, Bradford N. Pease, DeWitt C. Burkes and Charles H. Manlove. Drs. William K. Livingston and Martin A. Howard were the speakers, December 4, on "Diseases of the Arteries" and "Diseases of the Veins" respectively.

**Course on Diseases of the Chest.**—The University of Oregon Medical School and the Pacific Northwest Section of the American College of Chest Physicians offered a post-graduate course on diseases of the chest at the school, December 13-14. Chairmen at the sessions were Drs. Grover C. Bellinger, Salem; John E. Nelson, Seattle; Orval F. Swindell, Boise, Idaho, and Frank I. Terrill, Deer Lodge, Mont. Dr. Thomas M. Joyce, professor of surgery at the medical school, gave a lecture at a dinner meeting at the University Club on treatment in cancer of the esophagus.

### PENNSYLVANIA

**First State Health Institute.**—The Pennsylvania Department of Health, in cooperation with the Medical Society of the State of Pennsylvania, the state departments of public instruction, public assistance and welfare, the state dental and nursing organizations, the U. S. Children's Bureau and the

U. S. Public Health Service, will present a health institute in Harrisburg, January 8-10. Among speakers at the sessions will be:

Dr. John J. Shaw, state secretary of health, The Role of the Department of Health, Organized Medicine, Local Departments of Health and the Voluntary Agencies in the Modern Health Plan.  
Dr. Francis F. Borah, Secretary of the state medical society, Organized Health Program.  
Dr. Erval Richard, Health Service, the Federal Government and Community Health.  
Dr. LeRoy U. Gardner, Saranac Lake, N. Y., Public Health Aspects of Industrial Hygiene, and the Part of the Health Departments in the Problem.  
Dr. James R. Martin, Philadelphia, The Crippled Child.  
Dr. Ralph M. Tyson, Philadelphia, Child Health.  
Clair E. Turner, Dr. P. H., Cambridge, Mass., The Old and the New in Health Education.  
Dr. William D. Stroud, Philadelphia, The Social Component in Heart Disease with Special Reference to the Rheumatic Heart.  
Dr. Herbert C. Woolley, Philadelphia, The Deficient and Mentally Ill.

At a banquet Thursday evening Governor James and Dr. Howard E. Milliken, mayor of Harrisburg, will be guests, and speakers will be Dr. William W. Bauer, director, Bureau of Health Education, American Medical Association, Chicago, on "What the Public Is Thinking About Health"; Dr. Arthur T. McCormack, Louisville, Ky., "A Lifetime Spent in Public Health," and Mr. John McCullough, of the staff of the Philadelphia Inquirer, "Health Is News." At a luncheon Friday Dr. Nathan B. Van Etten, New York, President of the American Medical Association, will speak on "American Medicine Organizes for National Defense." The Bureau of Public Health Nursing of the state health department will conduct a maternity institute for registered nurses in Harrisburg, January 13-17, and one in Pittsburgh, January 20-24.

#### Philadelphia

**Society News.**—Drs. Louis H. Clerf and Arthur J. Wagers, among others, addressed the Philadelphia Laryngological Society, December 3, on "Photographic Study of the Larynx by Mirror Laryngoscopy" and "Case of Severe Epistaxis Presenting Problems as to Etiology, Determination and Origin and Methods of Control" respectively.—Drs. Clyde H. Kelchner, Allentown, Pa., and Morris A. Bowie, Bryn Mawr, Pa., addressed the Philadelphia Rheumatism Society, December 5, on "Fibrositis" and "Joint Physiology" respectively.—Dr. Waldo E. Nelson addressed the Philadelphia Pediatric Society, December 10, on "Role of Excessive Carbohydrate Intake in the Etiology of Diabetic Acidosis" and Drs. Francis C. Dohan and Francis D. W. Lukens, "Effect of Early Treatment in Experimental Diabetes."—Dr. John Scudder, New York, addressed the Philadelphia Urological Society, December 16, on "Shock: Blood Studies as a Guide to Therapy."

#### TENNESSEE

**Personal.**—Dr. Charles B. Roberts, Sparta, entertained the White County Medical Society recently at a dinner in honor of Dr. Sanford E. Gaines, Sparta, who has completed fifty years in the practice of medicine. The guest speaker was Dr. Charles E. Reeves, Gainesboro, who paid tribute to Dr. Gaines.—Dr. William B. Farris, Tazewell, has been appointed health officer of Williamson County to succeed Dr. Roscoe Faulkner, Batesville, Miss.—Dr. Warren C. Ramer, Trenton, has been appointed head of the Henderson-Decatur county health unit to succeed Dr. James C. Armstrong, now of Jefferson City, resigned.—Dr. Tinsley R. Harrison, Nashville, recently received the honorary degree of master of science from the University of Michigan Medical School, Ann Arbor.—Dr. John B. Youmans, associate professor of medicine, Vanderbilt University School of Medicine, Nashville, has gone to Europe as a member of the Health Commission of the Rockefeller Foundation, according to *Science*.

#### TEXAS

**Hospital News.**—Dr. Samuel M. Hill, Dallas, has donated a library wing to St. Paul's Hospital, Dallas. It will have a capacity of about 3,000 books and will be under the direction of a full time librarian.—Dr. Lucius R. Wilson, superintendent of the John Sealy Hospital, Galveston, since 1928, resigned to become superintendent of the Hospital of the Protestant Episcopal Church of Philadelphia, January 1.

**Woman Swindles Physicians.**—The J. B. Lippincott Company, Philadelphia, reports that a woman using the name of Tess Frazier is defrauding physicians in Texas by selling two year subscriptions to the *Digest of Treatment* for \$5, which is the subscription price for one year. Her technic appears to be to get renewals at a special price for cash in advance. The woman does not represent the Lippincott Company.

**Society News.**—Drs. Geneva Ernestine Smith and Elisha F. Meredith addressed the Dallas County Medical Society, Dallas, November 14, on "Diagnosis and Treatment of Pneumococcic Meningitis" and "Comparison in Treatment of Pneumonia in Children" respectively.—Dr. Joseph G. Gathings, Houston, among others, addressed the Hunt-Rockwall-Rains County Medical Society, Greenville, November 12, on "Gonorrheal Vulvovaginitis in Immature Females."

#### WASHINGTON

**Society News.**—The King County Medical Society met jointly with the Seattle District Dental Society, December 2, in Seattle with the following speakers: O. T. Dean, D.D.S., on "Local and General Anesthesia in Dentistry" and Dr. Edwin G. Bannick, "Problem of Focal Infections in Internal Medicine."—Dr. Otto M. Rott, Spokane, Wash., addressed the Walla Walla Valley Medical Society in November on "What Can Be Done to Prevent Deafness and to Aid the Hard of Hearing."—A program on heart disease was presented before the Whitman County Medical Society, Colfax, December 5, by Drs. Paul G. Weisman, Colfax, James L. Gilleland, Pullman, and Randall W. Henry, Endicott.

#### WISCONSIN

**In Honor of Dr. Frank Billings.**—Milwaukee Sanitarium at Wauwatosa has just dedicated its twentieth building and named it the Billings House in honor of the late Dr. Frank Billings of Chicago, who for twenty-five years was a director. Billings House is a beautiful home, the setting among the trees offering quiet, comfort and refinement to the patients. Dr. Billings was also for many years dean of the faculty of Rush Medical College, a Trustee of the American Medical Association and one of its former presidents. He died Sept. 20, 1932. The medical director of the Milwaukee Sanitarium is Dr. Rock Sleyster, who also is a former President of the American Medical Association.

#### GENERAL

**Changes in Obstetrics Board.**—Drs. Norman F. Miller, Ann Arbor, Mich., and Willard R. Cooke, Galveston, Texas, have been elected members, directors and examiners of the American Board of Obstetrics and Gynecology. They succeed Drs. Jennings C. Litzberg, Minneapolis, and Grandison D. Royston, St. Louis, who resigned, October 15.

**Bovine Tuberculosis Program Completed.**—The last two counties in the last state, California, have been certified as accredited counties in the twenty-three year testing program for the eradication of bovine tuberculosis, the U. S. Department of Agriculture announces. The degree of infection in every county in every state has now been reduced to less than 0.5 per cent, signifying virtual eradication. The task of testing cattle with tuberculin was begun in 1917 and has involved more than two hundred and thirty-two million tests and retests. About four million tuberculous cattle were removed for slaughter. During the campaign, a new tuberculin was developed for testing, which detects about 10 per cent more tuberculous animals than that used in early tests, it was pointed out. Continued retesting will be necessary, it was said, especially in herds from which infected animals have recently been removed. The late J. A. Kiernan, who died in 1927, was the first federal veterinarian in charge of the project and it has been continued under the direction of A. E. Wight.

**Physicians Warned of Narcotic Addict.**—Physicians are warned of a morphine addict who is a suspect in the murder of a physician in Detroit about twelve years ago. His description as reported by the Wayne County Medical Society reads: 37 years of age, 5 feet 5 inches tall; weight 110; sallow complexion; black hair; has scars on the left wrist and lower right limb which, he claims, are caused by osteomyelitis. The addict uses the names Robert McDonald, Paul Brown and Paul Murray, but his true name is said to be James Shannon. The man is also wanted by the government for violation of section 28 of the criminal code and for parole violation in Ohio. Detroit authorities recently traced Shannon to Toledo, but he eluded them, going to Louisville, Ky. Any one hearing of this person is asked to notify the local bureau of narcotics or Ralph H. Oyler, district supervisor, 802-810 Federal Building, Detroit.

**Physicians Complain of Book Agent.**—A physician from Kentucky writes that the International American Company, 201 North Wells Street, Chicago, has not been fulfilling its contracts made through an agent to sell encyclopedias for a fixed amount. The contract calls for \$29.50 for a set of eight

volumes of the *International American Encyclopedia* and stipulates that on completion of the payments one copy of Webster's *Unabridged Dictionary* will be sent to the purchaser. The contract reads "Pay Representative First Payment Only. Balance as Specified." One B. L. Martin has been the agent involved. One physician paid the amount in full and received neither the encyclopedia nor the dictionary, while others who paid partial amounts received one or the other. The Chicago Better Business Bureau has received similar complaints involving B. L. Martin. According to complaints in the bureau, Mr. Charles E. Knapp of the International American Company writes that Martin has limited authority to collect up to \$14.75 and that in those cases in which the amount had been paid in full Martin evidently had not sent in the orders.

**Accident Racketeer.**—A West Virginia physician recently reported a swindler who used a fracture to obtain money from an insurance company and absconded without paying his medical bills. The man, who was obese, rented an apartment in one of the modern buildings in Charleston. He called the physician late the first night with a story of having sat in a chair in his apartment, having fallen and hurt his back. He did not wish the physician to call, but visited the office the next day. A roentgenogram showed a fracture of the coccyx. He refused to stay in bed, made many calls to the physician's office and traveled to various towns in the vicinity to sell screen advertising. A second roentgen examination six weeks after the alleged injury showed the same fracture, the physician reported. Subsequently the "patient" made a settlement with the insurance company covering the liability of the apartment house and immediately departed with the check, which included allowances for the fees of the first physician consulted, an orthopedic surgeon and the roentgenologist. He also tricked some merchants with promises of screen advertising which never came and took small amounts of money from these men. The swindler gave his name as Arthur Loevin of Indianapolis, Los Angeles and New York.

**Sectional Ear, Nose and Throat Meetings.**—The annual sectional meetings of the American Laryngological, Rhinological and Otological Society are announced. The Southern Section will meet in Nashville, Tenn., January 8, with the following speakers, among others:

- Dr. Elmer James Mulligan, Baltimore, Treatment of Acute Frontal Sinus Infection.
- Dr. William de G. Mahoney, Nashville, Ménière's Syndrome.
- Dr. John J. Shea, Memphis, Tenn., Nasal Tumors of Pituitary Origin: Report of Case.
- Dr. Roy A. Barlow, Charles Town, W. Va., The Neglected Ethmoid Headache.
- Dr. Walter A. Wells, Washington, D. C., Danger to the Hearing Apparatus in Modern Warfare.

The Eastern Section will meet in Philadelphia, January 10, at the Bellevue-Stratford Hotel. The speakers will include:

- Dr. Wilfred D. Langley, Sayre, Pa., Allergic Rhinitis.
- Dr. Albert D. Ruedemann, Cleveland, "Pop-Eye."
- Dr. William D. Province, New York, Sulfathiazole.
- Dr. Karl Kornblum, Philadelphia, The Present Status of Roentgen Therapy in Sinusitis.

The Middle Section meeting will be at the Drake Hotel, Chicago, January 27, with the following speakers, among others:

- Melvin H. Knisely, Ph.D., Chicago, Dr. Warren K. Stratman-Thomas and Theodore S. Eliot, Ph.D., Memphis, Tenn., Microscopic Observations of the Changes in the Blood and Circulation in Living Animals.
- Stacy R. Guild, Ph.D., Baltimore, War Deafness and Its Prevention.
- Capt. Cole D. Pittman, Chanute Field, Ill., The Relation of High Altitude Flying and Rapid Changes of Atmospheric Pressure to Otolaryngology and Its Effect on the Middle Ear and Accessory Sinuses in Military Aviators.
- Dr. Paul H. Holinger, Chicago, Esophageal Perforations and Complications.

**The Academy of Orthopaedic Surgeons.**—The ninth annual convention of the American Academy of Orthopaedic Surgeons will be held at the Roosevelt Hotel, January 12-16, in New Orleans. The guest speakers will be:

- Drs. Ernst Bergmann and Arthur Krida, New York, Aseptic Necrosis and Bone Drilling.
- Dr. Edward W. Alton Ochsner, New Orleans, Thrombophlebitis and Postphlebotic Edema.
- Dr. Harold B. Boyd, Memphis, Tenn., Congenital Pseudoarthrosis.
- Dr. Murray M. Copeland, Baltimore, Classification of Bone Tumors According to Radiosensitivity.
- Dr. Edward A. LeCocq, Seattle, Use of Neosphenamine in the Treatment of Acute Osteomyelitis with Associated Staphylococcal Septicemia: A Clinical and Experimental Study.
- Dr. Gerald G. Gill, San Francisco, An Accurate Method for the Estimation of the Expected Growth of the Femur and Tibia in Individual Children.
- Drs. Allen F. Voshell and Otto C. Brantigan, Baltimore, Some Mechanical Derangements of the Knee.
- Dr. Beveridge H. Moore, Chicago, A Study of End Results in Bone Lengthening.
- Dr. J. Albert Key, St. Louis, Comparison of Stainless Steel and Vitallium as Material for Internal Fixation of Bone.

Dr. Norman T. Kirk, colonel, medical corps, U. S. Army, Washington, D. C., Organization for Evacuation and Treatment of War Casualties.

Dr. Alberto F. Inclan Jr., Habana, Cuba, Use of Preserved Bone Grafts in Orthopedic Surgery.

Dr. Robert D. Schrock, Omaha, will deliver his presidential address Wednesday afternoon, January 15. The program also includes a clinical program at Tulane University of Louisiana School of Medicine. Entertainment will consist of a cocktail party, reunion dinners and banquet.

**Symposium on Alcoholism.**—The Research Council on Problems of Alcohol sponsored a symposium on alcoholism December 27-29 in Philadelphia during the winter meeting of the American Association for the Advancement of Science. Subjects of the sessions were "Physiological and Chemical Considerations of Alcohol," "Clinical Aspects of Alcoholism," "Neuropsychiatric Features of Alcoholism," "Treatment and Prevention of Alcoholism" and "Social and Legal Problems of Alcoholism." The final session was a public meeting at which Dr. Thomas Parran, surgeon general, U. S. Public Health Service, Washington, D. C., was to preside and Dr. Abraham Myerson, Boston, was the speaker on "The Social Pharmacology of Alcoholism." Among the speakers at the sessions were:

- Dr. Andrew C. Ivy, Chicago, The Influence of Alcohol on the Alimentary System.
- Drs. Frederick A. Gibbs and Hollowell Davis, Boston, Electroencephalographic Changes Produced by Alcohol.
- Dr. Arthur W. Wright, Albany, N. Y., The General Pathology and Some Special Complications of Alcoholism.
- Dr. Anton J. Carlson, Chicago, The Need for Further Investigation of Alcoholism from the Standpoint of the Biological and Clinical Sciences.
- Dr. Foster Kennedy, New York, Neurological Conditions Encountered in Chronic Alcoholism.
- Dr. David Wechsler, Corona, N. Y., The Effect of Alcohol on Mental Activity.
- Dr. Robert V. Seliger, Baltimore, Treatment of the Alcoholic Addict.
- Dr. Bernard Glueck, Ossining, N. Y., A Critique of Present-Day Methods of Treatment of Alcoholism.
- Dr. Lawrence Kolb, U. S. Public Health Service, Washington, D. C., Alcoholism and Public Health.
- Edwin R. Keedy, LL.D., University of Pennsylvania Law School, Philadelphia, Alcoholism and Legal Responsibility.
- Donald S. Berry, National Safety Council, Chicago, Alcohol and Traffic Accidents.
- Dr. George S. Stevenson, medical director, National Committee for Mental Hygiene, New York, Education and Control of Alcoholism.

**Unlicensed Practitioner Held as Draft Evader.**—Physicians in West Virginia and Pennsylvania have reported the activities of a man who for months has been posing as a physician and is now being held as a draft evader. The man first appeared in the spring of 1940 at the headquarters of the West Virginia Medical Association, giving his name as S. S. Strauss and saying that he was a graduate of Long Island College of Medicine, Brooklyn, and that he was licensed to practice in West Virginia. He obtained positions doing relief work in various towns in the coal fields but disappeared when it became known that he was not licensed and had not graduated from the Long Island college. A notice in the *West Virginia Medical Journal* in October warned physicians to look out for Strauss. Immediately after publication of this notice "Dr." Strauss was found practicing, and when the article was shown to him he confessed that he was not a physician, according to the *West Virginia Medical Journal* for November. In the latter part of October a man who seemed to be the same appeared in a Pennsylvania town calling himself Charles F. Straub. A physician of whom he asked help in finding a position referred him to an opening in West Virginia. At this time the applicant said that he had graduated from Tulane University of Louisiana School of Medicine, had served an internship in Charity Hospital, New Orleans, had passed examinations of the National Board of Medical Examiners, and had had special training in pediatrics at Charity Hospital and at the Mayo Clinic, Rochester, Minn. Tulane and the Mayo Clinic reported they had no record of Charles F. Straub. A report, dated December 23, states that Strauss went to Kingwood, W. Va. The state police took him in custody as a suspicious character and discovered that, while his automobile license was in the name of Samuel Strauss, his draft registration card bore the name Kreiger. The police notified the U. S. Department of Justice, which sent back a police record dating from 1933. Names he has used include Seymour Rothchild, Seymour Davis Strauss, Milton Fenberg, Seymour Strauss, Samuel Liebowitz and Samuel Seymour Strauss. His activities have been carried on in California, Pennsylvania, Virginia, Ohio, Missouri, New York and West Virginia. They include sentences in various penal institutions for using the mails to defraud and one for vagrancy. The man was being held in jail in Kingwood for the next meeting of the federal grand jury on a charge of registering for the draft under an assumed name.

## Foreign Letters

### LONDON

(From Our Regular Correspondent)

Nov. 16, 1940.

#### A Bombed Hospital and Ambulance Depot

What happens when a direct hit occurs is shown in the press this morning. A hospital, an ambulance station and a nursing home were hit by bombs in a night air attack. At the hospital 7 patients and 1 sister were killed. A high explosive bomb crashed through a window on the ground floor of a block in which chronically ill patients—aged women, crippled and infirm—were housed. Five of these were killed outright and 2 others died later. The sister, who was in her office beside the window through which the bomb entered, was killed immediately. Other women in the hospital sustained slight injuries. Three bombs also fell in the hospital grounds and damaged the water supply.

In another district a school which was being used as a fire station and ambulance depot was wrecked by bombs. Several people, most of them firemen, were killed. The ambulance unit included several women, some of whom were in the basement of the building when the bomb exploded, but only 2 were injured. Nearly all the ambulances were destroyed. One ambulance driver was removing seriously injured firemen to a hospital when a second bomb exploded. It blew off the roof of his ambulance, but he continued on his journey and after handing over his patients collapsed from shock.

#### Casualties from Air Attacks on Britain

In the House of Commons the Prime Minister, Mr. Churchill, referred to Hitler's threat that on September 4, if we did not bend to his will, he would wipe out our cities. But they were still standing and were quite distinctive objects on the landscape, and our people were going about their tasks with the utmost activity. The casualties amounted to fourteen thousand civilians killed and twenty thousand seriously wounded, of which four fifths were in London. As against this, scarcely three hundred soldiers had been killed and five hundred wounded. The full malice of the enemy and his bombing force had been employed against us, but the scale of the attack had dwindled. The weekly average of casualties (killed and seriously wounded) for September was four thousand five hundred and for October three thousand five hundred. In the first week of the intensive bombardment of September there were six thousand casualties, in the last week of October only two thousand. The casualties have been nothing like the scale anticipated before the war. Great London hospitals singly made preparations to deal with as many as one thousand casualties from a single raid.

The official figures for the month of October, which have just been issued, show that six thousand three hundred and thirty-four civilians were killed and eight thousand six hundred and ninety-five injured and detained in hospitals. The killed consisted of two thousand seven hundred and ninety-one men, two thousand nine hundred women and six hundred and forty-three children under the age of 16 years; the injured, of four thousand two hundred and twenty-eight men, three thousand seven hundred and fifty women and seven hundred and seventeen children. The number killed in September was six thousand nine hundred and fifty-four and in August one thousand and seventy-five. The government is considering the question of insurance against the risk of death in air raids. Insurance companies are offering to insure against this risk at an annual premium of 1 per cent, but in the House of Commons a member asked the government to undertake the insurance at 0.1 per cent, which he claimed would yield large profits.

#### Ear Injuries in Warfare

At the Section of Otology of the Royal Society of Medicine a discussion took place on war injuries of the ear. Mr. Lionel Colledge said that the injuries caused by explosions were of two classes: those with gross tympanic injury and those of concussion of the labyrinth without signs of tympanic injury. Direct wounds of the temporal bone in war must be fairly common, but many were not recorded, probably because they were often immediately fatal. If a projectile could not be extracted through the meatus, the proper route was a retroauricular incision.

Miss D. Josephine Collier discussed ear injuries in the civil population during air raids, mainly on the basis of her experience in the Spanish civil war. Injuries of the middle ear could be divided into two groups, those produced by penetration of bomb fragments and those due to the expansion of air produced by the explosion. A foreign body should be removed only when it was producing severe reaction, such as pain and persistent discharge. Removal should be done by the radical mastoid operation as conservatively as possible. The majority of ear injuries treated at Barcelona were caused by blast: one hundred and seventy-five against thirty-three by bomb fragments. The majority of the injuries caused by blast occurred in the street, as walls of buildings gave protection. Rupture of the tympanic membrane was accompanied by sharp pain, bleeding from the ear and tinnitus. If the patient was seen during the short period of bleeding, drainage should be assisted by placing him on the appropriate side. The practice of placing a pipe or pencil between the teeth when a bomb was expected to fall was found to diminish the incidence of tympanic injuries. The ear protector which gave the best results was a plug with a valve that remained open save when the external pressure was increased.

Mr. V. E. Negus said that of six hundred and twenty-two civilian air raid casualties one hundred and ninety-nine were injuries of the head and neck, and of these one hundred and twenty-nine were craniocerebral. The ear cases numbered twenty-four (3.8 per cent). In military casualties the percentage was 2. The majority of the ear injuries were rupture of the tympanic membrane. Practically all the ear injuries were associated with others, and the majority were due to blast. No patient complained to any extent of tinnitus or vertigo, and routine examination was required to discover some of the ruptures. The examination was made in view of the serious effects that might follow infection of the ear. For cleansing the external meatus he preferred a mercury preparation which left the ear dry, moisture being liable to precipitate infection. Any cerumen should be carefully removed, but the deeper parts of the meatus should be left severely alone. He protested against the practice of pushing wicks of gauze or other material into the ear. At one time the case for immediate operation in wounds of the mastoid process might have been arguable, but the introduction of chemotherapy pointed to the wisdom of delayed operation. Any fragments of loose bone or metal should be removed at the time, but nothing in the way of extensive operation should be done.

#### The Native Physician in the British Western Pacific

The *Native Medical Practitioner*, which is the journal of the Central Medical School, Suva, shows the progress which has been made in educating the natives of the Pacific in modern medicine. The students are drawn from the islands of the British Western Pacific, New Hebrides, Tonga, New Zealand dependencies and American Samoa. The course takes four years and the graduates are termed "native medical practitioners." They are under the control of the medical authorities of the various islands. In a foreword to the journal Sir Harry Luke, governor of Fiji and high commissioner for the Western Pacific, pays a tribute to the work of Dr. S. L. Lambert and the Rockefeller Foundation. The graduation ceremony of the



year is described by a Fijian student. The Hippocratic Oath is administered in the presence of a representative gathering of officials and the public. The governor stated that he had observed with satisfaction the patience and skill of the native medical physicians. The articles in the journal show how well modern teaching has taken root in this remote part of the world. A nurse, who gained second place in the British Empire Baby Week Campaign, describes how child welfare work is actively carried on in Fiji. Routine medical inspection and advice to parents on the lines of modern teaching are described. An article on his surgical experiences by a native graduate shows sound surgical instruction. The high proficiency of the native students in anatomy is borne out by medical visitors to the school. The lecturer on dentistry describes the superiority of the native teeth to those of Europeans. The superiority of the native teeth is ascribed to diet, and the cases of caries are deemed to be caused by the eating of white bread. Tuberculosis in Fiji is dealt with by Dr. McGusty, director of medical services. The disease is on the wane but is still a serious problem.

## BUENOS AIRES

(From Our Regular Correspondent)

Nov. 8, 1940.

### Health Regulations Governing Airships

According to new health regulations adopted by the government for commercial airships plying between foreign countries and Argentina, pilots must keep official records of the crew, passengers, merchandise, mail, landing stations en route, the occurrence of illness and so on. The record must show the visé of the Argentine consulate at the point of departure. There are also control regulations for the vaccination of the personnel.

### Health Service by Airship

By order of the Argentine government, a health service by airship has been inaugurated. It has exclusive use of three airships, with the same number of airports situated in the large Chaco region. The control of this service is divided between the national public health department in medical matters and the general office of civil aeronautics in matters of technical operation. When officially used, this service meets sanitary or prophylactic needs affecting public emergencies or makes possible medical aid for indigent persons. For this service there are no charges. The service may also be engaged on a private basis for ambulance purposes. Payment for this is at the rate of 50 centavos (14 to 15 cents) per kilometer. Until special funds enabling a special personnel are available, the requisite crews are furnished by the joint managements.

### Congress on Endocrinology

The second Pan American Congress for Endocrinology will meet in Montevideo, Uruguay, March 5-8, 1941. Among others, papers will be read by F. C. Koch, Chicago; H. M. Evans, California; B. A. Houssay, Buenos Aires, on the regulation of the endocrine functions of the pancreas; A. Lipschuetz, Santiago de Chile, on endocrine foundations in tumors of epithelial and mucosal origin in the female genital sphere; M. R. Castex and associates, Buenos Aires, on endocrine therapy in genital dysfunction; J. C. Mussio Fournier, c. s., Montevideo, on the cardiovascular apparatus in thyroid gland insufficiency; E. Miray López, Habana, on instantaneous perception of endocrine psychoses; A. Peralta Ramos, Buenos Aires, on endocrine correlation in disturbances of the genital cycle; L. Fraenkel, c. s., Montevideo, on mammary glands and endocrine glands: neurohumoral relations.

Dr. Pedro A. Barcia, Casilla de Correo 255, Montevideo, Uruguay, will furnish further information on request.

The meetings of the second Brazilian Congress for Urology were set for November 9-16 in Rio de Janeiro and São Paulo.

## First Argentine Congress for Puericulture

The first national congress for puericulture met October 7-12 in Buenos Aires under the presidency of Dr. Alfredo Buzzo, professor of toxicology in the medical faculty of Buenos Aires and a pediatrician. The chairman pointed out that ignorance and poverty were the two chief factors that caused untold misery to mothers and children. Maternal care and child care have been under legal control since 1936 (*THE JOURNAL*, April 27, 1940, p. 1684). He discussed nutrition, the norms for weaning, the use of biometry, the study of the preschool child and related topics. An exhibit of numerous charts showed the progress made by public and private institutions for infants and preschool children, as well as that of medicosocial welfare in Argentina.

The first of the leading subjects was the control of tuberculosis (Prof. Pedro de Elizalde). A number of papers were read dealing with the results of BCG vaccination. One of the papers on tuberculosis was by S. R. Rosenthal, Cook County Hospital, Chicago. The third leading subject dealt with growth and physical development. Prof. Pedro Escudero called attention to the fact that the potentialities, rhythm and character of physical development depended on nutrition. He discussed the factors which affected the normal development of the child during the first three years, such as heredity, diseases of parents, the care and nutrition of pregnant women and the care of the newborn. Other leading subjects were rickets, treated by Prof. Juan P. Garrahan and Felipe González Alvarez, and prevention of syphilis, discussed by Prof. Raúl Cibils Aguirre and Benito Soria.

The government was requested to create a special committee which is to give its cooperation to agencies working for the protection and medicosocial welfare of children. The government was requested to provide funds for the control of tuberculosis throughout the country. Organizations concerned with child protection are to interest themselves in the treatment of syphilitic fathers. The law requiring premarital examinations of men should be applied also to women. The physical and mental development of preschool children, especially among the underprivileged, should be supervised and kindergartens and schools for mothers established. Special courses for the training of teachers of abnormal children should be established by the department of justice and public instruction. The preparation of a health manual is desirable and should be used in all institutions connected with child welfare work.

In connection with the meeting of the congress, the National Institute for Nutrition, under the direction of Professor Escudero, released three pamphlets intended for the public. The first of these gave an insight into the work done by the institute, the second dealt with the problems of nutrition during pregnancy and the third discussed nutrition during the early years.

The next congress will meet in Córdoba in 1942.

## Marriages

ROBERT BRUCE MILLER to Miss Verna Anderson, both of Lebanon, Ore., in Albany in September 1940.

ROLAND E. NIEMAN, Cincinnati, to Miss Cynthia Hampton of Hamilton, Aug. 30, 1940.

HARRY SACKS, Washington, D. C., to Miss Isabell Boaz of Atlanta, Ga., Nov. 20, 1940.

AMBROSE J. HERTZOG to Miss Irma Behrens, both of Eau Claire, Wis., Oct. 11, 1940.

AUGUST C. PAVLOTOS, Lancaster, Pa., to Miss Grace Kusupolos in October 1940.

ERVIN T. RECHLICZ, Milltown, Wis., to Miss Doris Sylling of Amery, Sept. 24, 1940.

CLARENCE A. VOGEL to Miss Ada E. Smith, both of Elroy, Wis., Sept. 14, 1940.

## Deaths

**Roger Brooke** \* Assistant Surgeon General, Medical Corps, United States Army, with rank of Brigadier General, and Commanding Officer, Field Service School at Carlisle Barracks, Pa.; Baltimore Medical College, 1900; commissioned in the United States Army in 1901; was chief of the medical service of the Letterman General Hospital, San Francisco, from 1911 to 1915 and from August 1935 to April 1940; senior instructor in the medical officers training corps at Fort Oglethorpe, Ga., 1917-1918; chief of the section on tuberculosis in 1919 and chief of the division of medicine, Surgeon General's Office, War Department, 1920-1921; chief consultant, division of medicine, Veterans Bureau, Washington, D. C., in 1923; promoted to lieutenant colonel in 1917, colonel in 1927 and brigadier general in 1938; awarded the Distinguished Service Medal for services during the World War; fellow of the American College of Surgeons and the American College of Physicians; in 1938 member of the House of Delegates of the American Medical Association; aged 62; died, Dec. 18, 1940, in the Walter Reed General Hospital, Washington, D. C., of arteriosclerosis.

**John Shelton Horsley Jr.** \* Richmond, Va.; Harvard Medical School, Boston, 1922; member of the Southern Surgical Association; member and secretary, 1927-1928, of the Southern Society of Clinical Surgeons; associate professor of surgery at the Medical College of Virginia; on the staffs of the Medical College of Virginia hospitals, St. Elizabeth's Hospital, Sheltering Arms Hospital, Crippled Children's Hospital and the Retreat for the Sick; co-author of "Diagnosis of Diseases of the Stomach and Duodenum" and "Operative Surgery," fourth edition published in 1937; aged 40; was killed, Nov. 22, 1940, in an automobile accident.

**Ernest Amory Codman** \* Boston; Harvard Medical School, Boston, 1895; member of the American Surgical Association, American Association for the Surgery of Trauma, Society of Clinical Surgery and the New England Surgical Society; fellow of the American College of Surgeons; at various times assistant in surgery, assistant in clinical and operative surgery, and lecturer in surgery at his alma mater; consulting surgeon to the Massachusetts General Hospital; author of "The Shoulder"; aged 70; died, Nov. 23, 1940, in Ponkapog, Mass.

**Alfred George Long** \* Indianapolis; Manitoba Medical College, Winnipeg, Canada, 1908; director of the laboratory of hygiene, state board of health, from June 1922 to June 1924; formerly assistant professor of bacteriology and pathology and acting director and director of the public health laboratories, University of North Dakota School of Medicine, Grand Forks; aged 54; died, Nov. 20, 1940, of carbon monoxide poisoning.

**Robert Baylor Shackelford** \* Lieutenant Colonel, United States Army, retired, Cismont, Va.; University of Virginia Department of Medicine, Charlottesville, 1909; served during the World War; was commissioned a major in the medical corps of the United States Army in 1920 and was retired with rank of lieutenant colonel in 1931 for disability in line of duty; aged 59; died in November 1940 at West Point, N. Y.

**Lewis Morris** \* Medical Director with rank of Captain, U. S. Navy, retired, Whitefield, N. H.; University of Maryland School of Medicine, Baltimore, 1890; entered the navy in 1891 and retired in 1920 for incapacity resulting from an incident of service; served during the Spanish-American and World wars; aged 73; died, Nov. 15, 1940, in the Knickerbocker Hospital, New York, of chronic nephritis and uremia.

**John Willis Martin** \* Annapolis, Md.; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1917; fellow of the American College of Surgeons; served during the World War; on the staff of the Emergency Hospital; aged 44; died, Nov. 5, 1940, in Eastport of a brain tumor.

**John Crandall Lindsay** \* Cheshire, Conn.; Harvard Medical School, Boston, 1910; member of the American Psychiatric Association and the New England Society of Psychiatry; medical director of the Connecticut Reformatory; aged 57; died, Nov. 16, 1940, in the New Haven (Conn.) Hospital of chronic duodenal ulcer.

**Frederick Ammi Mead**, Willimansett, Mass.; Albany (N. Y.) Medical College, 1892; member of the Massachusetts Medical Society; served during the World War; for many years member of the board of health of Chicopee; aged 71; died, Nov. 14, 1940, in Chelsea.

**Ernest H. McDede**, Lyndhurst, N. J.; College of Physicians and Surgeons, Baltimore, 1910; member of the Medical Society of New Jersey; formerly member of the board of health and board of education; for many years on the staff of the West Hudson Hospital, Kearney; aged 60; died, Nov. 3, 1940.

**John Cotton Maynard**, Toronto, Ont., Canada; University of Toronto Faculty of Medicine, 1914; served during the World War; attending physician to the Home for Incurable Children; member of the board of governors of the Trinity College School, Port Hope; aged 48; died, Nov. 7, 1940.

**Dean Loller Rider** \* Riverside, Ill.; Rush Medical College, Chicago, 1923; clinical assistant in surgery at his alma mater from 1923 to 1928 and clinical associate from 1928 to 1937; formerly on the staffs of the Provident and Cook County hospitals; aged 42; died, Nov. 15, 1940.

**Frank M. Lander**, Williamston, S. C.; Medical College of the State of South Carolina, Charleston, 1900; member of the South Carolina Medical Association; formerly member of the state board of medical examiners; aged 67; died, Nov. 3, 1940, in Anderson.

**Alexander Eustace Muse**, Baltimore; Maryland Medical College, Baltimore, 1904; member of the Medical and Chirurgical Faculty of Maryland; also a pharmacist; aged 76; died, Nov. 18, 1940, in St. Agnes' Hospital of carcinoma of the prostate.

**Charles Sims Miller**, Jackson, La.; Medical Department of Tulane University of Louisiana, New Orleans, 1910; acting superintendent of the East Louisiana State Hospital; aged 54; died, Nov. 7, 1940, in Memphis, Tenn., of coronary thrombosis.

**Peter McPartlon**, Schenectady, N. Y.; Albany Medical College, 1900; member of the Medical Society of the State of New York; formerly superintendent of the Glenridge Sanatorium; aged 68; died, Nov. 20, 1940, in the Ellis Hospital.

**Edward Browning Meigs** \* Washington, D. C.; University of Pennsylvania Department of Medicine, Philadelphia, 1904; an Associate Fellow of the American Medical Association; aged 61; died, Nov. 5, 1940, of pulmonary tuberculosis.

**Charles Eugene Mayfield**, Wanatah, Ind.; Kentucky School of Medicine, Louisville, 1905; member of the Indiana State Medical Association; formerly county coroner; aged 59; died, Nov. 3, 1940, of carcinoma of the prostate.

**Henry Thomas Lee**, New York; Columbia University College of Physicians and Surgeons, New York, 1898; aged 68; died, Nov. 17, 1940, of injuries received when he fell from an eighth floor window of the Doctors Hospital.

**Floyd Britton Langdon**, Des Moines; University of Illinois College of Medicine, Chicago, 1915; on the staffs of the Iowa Lutheran, Iowa Methodist and Mercy hospitals; aged 50; died, Nov. 10, 1940, of cerebral hemorrhage.

**Henry Isaac Leviton** \* Los Angeles; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1909; aged 56; on the staff of the Cedars of Lebanon Hospital, where he died, Nov. 11, 1940.

**Moe Jesse Mayer**, New York; New York Homeopathic Medical College and Flower Hospital, New York, 1916; aged 49; died, Nov. 7, 1940, in the Beth David Hospital of arteriosclerotic heart disease.

**William Edward Owen**, Cedar Rapids, Iowa; Rush Medical College, Chicago, 1889; member of the Iowa State Medical Society; aged 78; died, Nov. 9, 1940, of abscess of the liver and bronchopneumonia.

**Homer Benjamin Millhon** \* Owaneco, Ill.; Northwestern University Medical School, Chicago, 1903; for many years on the staff of St. Vincent's Hospital, Taylorville; aged 70; died, Nov. 2, 1940.

**Irving Isaac Littman** \* Baltimore; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1928; aged 37; died, Nov. 2, 1940, of cerebral embolism.

**Francis Kirsch**, East St. Louis, Ill.; Homeopathic Medical College of Missouri, St. Louis, 1890; aged 78; died, Nov. 5, 1940, in St. Mary's Hospital of cerebral hemorrhage.

**John Powers**, Kansas City, Mo.; Missouri Medical College, St. Louis, 1881; aged 81; died, Nov. 7, 1940, of arteriosclerotic nephritis with uremia.

**William John Morrison**, Chicago; Chicago Medical School, 1916; aged 59; died, Nov. 13, 1940, of acute myocarditis.

**Mark Manley** \* Brooklyn; Long Island College Hospital, Brooklyn, 1895; aged 72; died, Nov. 7, 1940.



## Bureau of Investigation

### BRADFORD, BROUGH, DOYLE AND DAVIS

#### Various Doctors Connected with Promotion of Fraudulent Obesity Cure

The recrudescence of a fake "fat cure" that apparently had been dormant for years is revealed in a Post Office fraud order banning from the mails a Baltimore outfit, The Bradford Laboratories, Marie Cecil, and their officers and agents.

The history of this fraud or its antecedents dates back at least forty years. Records show that H. Clark Bradford, M.D., was advertising his obesity treatment from New York in 1900. Bradford died in 1915 and his business was taken over by one F. Thompson Brough, M.D. For a time Brough called himself "Successor to Dr. H. C. Bradford" and claimed that he was "prescribing by the Bradford Method." In addition to his "obesity cure" business Brough had at different times conducted other quackish activities, numerous and varied.

# OBESITY

## To Fat People:

**I can reduce your weight 2 to 5 pounds a week without any radical change in what you eat; no nauseating drugs, no tight bandages, nor sickening cathartics. I am a regular practising physician, making a specialty of the reduction of surplus flesh; and after you have taken my treatment a few weeks you will say: "I never felt better in my life."**

### SAFE, PROMPT AND CERTAIN.

**By my treatment your weight will be reduced without causing wrinkles or flabbiness of skin; heavy abdomen, double chin or other evidences of obesity will disappear; your form will acquire symmetry; complexion will be cleared; troubles of heart, kidneys, stomach or other organs will be remedied; and you will be delightfully astonished at the promptness and ease with which these results are accomplished under my system. Write for my new pamphlet, which will be sent sealed in plain envelope. It will convince you. Mention Cosmopolitan when writing.**

**H. C. BRADFORD, M.D.,**

American Tract Society Building,  
150 Nassau Street.

**NEW YORK**

Advertisement of original Bradford concern from the *Cosmopolitan*, November 1900.

Presumably Bradford's "cure" retained its old composition. When Bradford was putting it out, the American Medical Association's chemists made some tests for thyroid content but found none. The chemists did report that in general the "S. Z. Special Tablets" appeared to contain baking soda, some bismuth salt, perhaps a subnitrate, and some nitrogenous principle, perhaps pancreatin. The "A. R. Special Tablets" appeared to contain baking soda and rhubarb or some similar cathartic. In 1911 the state chemists of North Dakota reported finding that the "A. R. Special Tablets" contained powdered rhubarb, baking soda and oil of peppermint, and the "S. Z. Special Tablets" benzoin, extract of nux vomica, potassium carbonate and a bismuth salt.

In 1930 it was reported that Brough had died from poison, self administered, after having been indicted on a charge of performing an abortion. It was said that he had taken over the "practice" of another physician who had "retired" from the abortion field after having trouble with the authorities.

Whether Brough continued operating the "fat cure" business up to the time of his death in 1930 is not clear. At least it

appears that thereafter the project was dormant until 1936, when it was reported that a concern known as the Bradford Laboratories was advertising a reducing method from Baltimore. Its literature claimed that "for over half a century we have been in business" and that "The Bradford Method of Weight Reduction has successfully reduced the weight of many people over a period of fifty years." Included in the advertising was a "treatise" on obesity written by F. Thompson Brough of New York. This literature did not reveal that Brough had been dead since 1930. There was also an "absolute guarantee" issued over the facsimile signature of Frank J. Doyle, M.D., "Medical Director."

In 1938 a physician reported that the Bradford Laboratories, answering an inquiry that he had sent them, replied in part:

"We wish to advise that the same preparations used by Dr. Brough in 1916 are still in use today."

Hence the treatment presumably still contained, among other ingredients, such chemical substances as baking soda, potassium carbonate and a bismuth salt. Yet in a letter sent out in June 1938 to an inquirer the Bradford concern claimed:

"The treatment is composed of a combination of roots and herbs, no chemical preparations . . ." (Italics ours.—Ed.)

Although, as previously mentioned, F. Thompson Brough died in 1930, a medical society reported in April 1938 that some one was putting out "F. Thompson Brough's Treatment for Obesity" from Eighth Avenue and Thirty-Fourth Street, New York, an address that Brough had long used in selling his mail order "treatment."

In 1938 the Post Office Department began to look into the Baltimore concern's activities. The information that follows is taken partly from the memorandum on the case by Judge Vincent M. Miles, solicitor for the department, and partly from the files of the Bureau of Investigation of the American Medical Association.

The Post Office investigation revealed that an Elmer L. Kincaid was both president and vice president of the Bradford company; his brother, a Donald Kincaid, was acting manager, secretary and treasurer, and Dr. William A. Davis was "Medical Director," as successor to Dr. Frank J. Doyle, who died in February 1939 and who himself had succeeded Dr. F. Thompson Brough in this position. Also it was found that in spite of the "Laboratories" part of the name the firm did not have equipment for compounding medicines. It was shown that although the advertising advised that an "experienced" physician should be chosen for the treatment of obesity, one of the promoters admitted that both Drs. Doyle and Davis had been employed through advertisements in the local papers and had no special qualifications or experience in treating obesity.

Among the Bradford advertising claims that the Post Office memorandum on the case pointed out as typical were:

Proven by over fifty years of success.

Called "The World's Greatest Treatment for Obesity."

This method is unlike any other.

The fatty tissues must be gradually dissolved and eliminated from the system . . . our treatment is the one that does it . . . removal of diseased fatty tissue is but one detail of the treatment; it is quite as important that the health should be improved, that the blood and skin be purified, that "crow's feet," wrinkles, etc., be cleared from the skin, that the eyes be given the lustre of true health and that the whole physical and mental system shall be brought to a high standard of health.

Ladies oftentimes write that they only want a reduction in the sizes of certain parts of the body, while others desire a general reduction in all parts. Our treatment is so regulated that this result is usually readily accomplished.

The Post Office hearing brought out that, though it was claimed that the "remedies" were selected to meet the "specific requirements" of each patient, and though the late Dr. Doyle, when "Medical Director" of the business, had claimed that he carefully examined blanks filled out by customers and prescribed proper treatments on the basis thereof, he nevertheless had admitted that these blanks did not "mean much." Expert medical testimony was presented to show that the so-called "report blank" did not call for sufficient information to enable the Bradford people to prescribe a sure, safe or permanent means of overcoming obesity in the person involved. Dr. Davis, testifying for the company as successor to Dr. Doyle, even admitted that "personal contact" with the patient was necessary in the successful diagnosis of certain conditions such as appendicitis, which, if present in persons taking the Bradford treatment, might cause

grave and even fatal results, and that in diagnosing appendicitis in regular practice he resorted to a blood test, urinary examination and other procedures not included in his Bradford method. While he claimed that the Bradford treatment was not sold in any case in which the patient's blank gave any indication of appendicitis or pregnancy, other evidence showed that patients might not always furnish such indications in filling out the forms.

The treatment was shown to consist of forty-five weekly assortments of stock tablets, and a "massage lotion." There were also a printed "Private Manual of Instructions" and a stereotyped set of further directions. Despite the presale representations that the treatment suited the "specific requirements" of each purchaser, both Dr. Doyle and Mr. Donald Kincaid admitted that all patrons were given identical medicines for the first five weeks. In fact, it was shown that the only variation in the preparations furnished to different persons during the entire forty-five week period consisted in the substitution in some cases of a weaker or stronger form of laxative, dependent on the age and the number of bowel movements reported by the customer, and in an occasional increase or decrease in dosage.

The expert medical testimony also showed that the treatments, somewhat varied from week to week, included fucus and poke root (common ingredients of commercial "obesity cures" but largely discredited for the purpose) as well as ordinary laxatives, purgatives and cathartics, including sodium bicarbonate, jalap, aloes, calomel, croton oil, podophyllum, epsom salt and gamboge. It was pointed out that, although purgatives have for centuries been used for reducing, scientific investigation and accumulated experience have shown that such use is unsuccessful for that purpose and the results are principally harmful.

Further, the expert testimony showed, the Bradford method would not quickly, easily, safely or permanently eliminate obesity regardless of the duration or difficulty of the case, as claimed by the promoters, because experience has shown that treatments of this kind are not a reliable or effective means of overcoming the disturbance of metabolism responsible for that condition; that the excessive loss of fluid with stools that results from the use of these purgatives is quickly restored; that the treatment would not fit every case or remove fat from the breasts, hips, eye sockets, legs or other special parts of the body played up in the advertising; and that, despite the presale representations to the contrary, the patient would be left with wrinkles, crow's feet, "bags" and flabbiness. Neither would the treatment overcome nervousness, appendicitis, eczema, rheumatism, liver, kidney, bladder or heart disorders, apoplexy, arthritis, impure blood or some other conditions, as claimed.

On the contrary, the expert medical testimony showed that harmful results might accrue to a person who took this treatment, depending on the diseases from which he might be suffering, and that some obese persons are tuberculous, in which case the Bradford method might prove particularly harmful in breaking down resistance and thus aggravating the malady. Further, it was shown that the drugs in the Bradford system have a highly irritating effect on the gastrointestinal tract and may cause nausea, acute gastritis, contractive spasm of the gall-bladder, enteritis, colitis, rupture of an infected appendix followed by peritonitis, and other serious results. Also it was emphasized that the exercises advocated by the Bradford concern might be dangerous in cases of obesity, complicated heart or kidney diseases, diabetes, thrombosis, phlebitis and other conditions commonly associated with obesity. It even was shown that the Bradford circulars urging the banishing of fat had been sent to persons whose inquiries had indicated the possible presence of pregnancy, ovarian or pituitary dysfunction, cardiovascular-renal failure and other ailments.

Dr. William A. Davis, testifying as "Medical Director" of the Bradford concern, stated that he was a graduate of the University of Maryland Schools of Pharmacy and Medicine "about 1898," served for five years as associate instructor of biology, anatomy and histology in Baltimore Medical College, took postgraduate work in general medicine, including diagnosis in the clinic and dermatology, spent some time at the University of Vienna clinics, and was a deputy health officer in Baltimore and in general practice in that city. Nevertheless, evidence presented showed that, like Dr. Doyle, he had tied up with the Bradford outfit through its advertisements.

In his testimony Dr. Davis admitted that he did not "know much" about metabolism and could not explain the physiologic changes in the body during the process; that he was not qualified as an endocrinologist, could not give the "full gamut" of the endocrine glands or name the chemical substances present in fat, and did not know the basis used in determining a calory. Though he claimed to be an expert on drugs, he failed on cross examination to answer correctly certain questions put to him regarding properties and dosages thereof, and admitted that in his practice he had never used the drugs contained in the Bradford treatment. He further admitted that they constituted an eliminative process (in spite of the disparagement of such a method of reducing in the Bradford literature) and that he was unable to cite any specific authority on obesity which featured the use of alteratives for that condition, having himself, in fact, used alteratives (such as the iodine in fucus) for increasing

BRADFORD LABORATORIES		
PROVEN BY OVER FIFTY YEARS OF SUCCESS	Distributors of Bradford Method for Obesity 38 HOPKINS PLACE, BALTIMORE, MD.	CLAIMED "THE WORLD'S GREATEST TREATMENT FOR OBESITY"
A PERSONAL MESSAGE OFFERING FREE PROOF YOU CAN REDUCE		
Dear Friend:		
ARE YOU INTERESTED IN THE REDUCTION OF YOUR WEIGHT? In improving your General Health? In Making your own Appearance More Attractive? In Winning and Holding Admiration and Love?		
If so, it would be a privilege for us to send you the latest edition of a new book revealing amazing and startling facts on OBESITY TOGETHER with a three day "PROOF TREATMENT". The entire package prepaid and ABSOLUTELY FREE TO YOU. The acceptance of this unusual GIFT places you under no obligation whatsoever--either now or at any other time.		
People who have for years been the hopeless victims of layer upon layer of heavy burdensome unsightly fat, daily endangering their health weakening their vitality and often subjecting them to ridicule; not only those, but hundreds of people are frankly astonished at the marvelous and puzzling disclosures which you may now obtain for the asking.		
This FREE PACKAGE once in your hands, should prove the first step towards a SAFE REDUCTION IN WEIGHT, a wonderful improvement in your general health--in your spirits--your appearance--even the lengthening of your life. No matter what you have tried in the past, no matter what you have seen or heard, here is an opportunity for you to get the result, AT NO EXPENSE TO YOU, whatever. This offer is being sent to you at the request of one of your friends who has taken the treatment and has reported they have had very satisfactory results from use of same.		
The SPECIAL FREE PACKAGE is now ready for mailing to you. On account of the cost of its preparation, postage and handling, please enclose ten cents in stamps or coin to help cover costs. BUT DO NOT DELAY, every day counts and time is fleeting: If you want to reduce excess flesh, be rid of fat, improve your health, enjoy greater comfort, vitality ease and increase your style and attractiveness -- SIGN AND MAIL COUPON BELOW--AT ONCE--Expecting an immediate reply, we are Very truly yours, Bradford Laboratories Dr. J. J. Doyle Medical Director		
BRADFORD LABORATORIES - 38 Hopkins Place - Baltimore, Md. Sign: Enclosed please find ten cents (stamps or coin) for which send me confidentially at once the new Free Package for Obesity in Plain Wrapper. This places me under no obligation whatever. NAME..... STREET OR R.F.D..... CITY OR TOWN.....STATE.....Dept 708		

Form letter (greatly reduced) sent out by the Baltimore Bradford concern.

weight rather than reducing it. He confessed that he was not familiar with the functions of the thyroid gland and that the elimination of fat would not conquer appendicitis, loss of sexual vigor, apoplexy and other conditions as alleged in the Bradford advertising. Altogether Dr. Davis's testimony showed that he was not well informed on the scientific treatment of obesity or on the disturbances of metabolism and glandular functioning which he admitted are responsible therefor.

As the acceptable evidence in the case showed that the business in question was a scheme for obtaining money through the mails by means of false and fraudulent pretenses, representations and promises, a fraud order was issued on Dec. 1, 1939, against the Bradford Laboratories, Marie Cecil and their officers and agents as such, debarring them from further use of the mails.

It may be worth mentioning in this connection that from the Bradford address, 38 Hopkins Place, Baltimore, Marie Cecil also conducted a cosmetic business, chiefly playing up "Solva Roma," an alleged depilatory, but there was also "Clax Pelets (for constipation and excess fat)" which Marie Cecil was advertising in 1928 from New York, where she was then conducting her business. In 1933 it was reported that a New England girl was severely burned after applying Solva-Roma to her face.

## Correspondence

### BONE MARROW TRANSFUSIONS

To the Editor:—In reply to many inquiries concerning the article "Bone Marrow Transfusion," published in the November 16 issue of THE JOURNAL, it would not be amiss to point out that a new method of therapy was presented. Since publication, more than sixty bone marrow transfusions have been done in cases of leukemia, myelogenous and lymphatic, and aplastic anemias. Since the series of cases is so small, conclusions cannot be drawn. However, the results are encouraging in that one noted a definite trend toward improved maturation and delivery of the bone marrow cells with the production of clinical and hematologic remissions. For this reason we are continuing bone marrow transfusions in the treatment of the deficiency blood dyscrasias.

The present status of the case reported (the first of our series and not a selected one) is as follows:

The patient was seen again on June 10, 1940. He had lost much weight on a reducing diet and had been doing well clinically and hematologically. On August 7 it was noted that evidences of a bleeding tendency had developed, e. g. generalized petechiasis, and a large spleen was felt one hand's breadth below the costal margin. The bone marrow had reverted to its original aplastic state. About one week later he died. Permission for autopsy was not obtained. The patient had not been given additional transfusions of bone marrow.

We justifiably felt that the original diagnosis should have been acute leukemic myelosis and not idiopathic aplastic anemia. However, this question is not germane to the discussion. Suffice it to say that a remission had been observed. Whether this remission was normal or induced will remain unanswered until more cases have been studied.

MAURICE MORRISON, M.D.

A. A. SAMWICK, M.D.

Brooklyn.

### LACTIC ACID IN THE ORAL CAVITY

To the Editor:—W. D. Miller (*Arch. f. exper. Path. u. Pharmacol.* 16:291, 1882; *The Micro-Organisms of the Human Mouth*, Philadelphia, S. S. White Company, 1890) enunciated his chemioparasitic theory of dental caries more than fifty years ago. He related dental decay to the production of acids resulting from the action of micro-organisms on carbohydrates. One of the acids stressed in this connection was lactic acid.

While Miller and many others have made numerous in vitro experiments showing the production of acids by oral micro-organisms, it is only recently that such in vivo experiments have been performed. Miller and Neuwirth (*Dental Cosmos* 77:453 [May] 1935) showed that the continual sucking of hard candies resulted in tooth decalcification. They found that the hard candies were composed of practically pure sucrose. They postulated that the tooth decalcification resulted from the action of organic acids on the tooth, the organic acids in turn coming from the action of salivary enzymes and bacteria on the sucrose. (See also in this connection *Dental Lesions and Systemic Disease*, editorial, THE JOURNAL, July 17, 1937, p. 211.)

Stephan (*J. Am. Dent. A.* 27:718 [May] 1940) showed a marked fall in the  $pH$  of plaques and open tooth cavities immediately following the rinsing of the mouth with certain carbohydrate solutions. However, Stephan did not indicate what acid or acids are responsible for the fall in  $pH$  noted in his experiments.

Employing the delicate method of Miller and Muntz for the precise determination of ultramicroquantities of lactic acid (*J. Biol. Chem.* 126:413 [Nov.] 1938), Profs. Isaac Neuwirth and J. A. Klosterman (*Proc. Soc. Exper. Biol. & Med.* 45:464 [Oct.] 1940) report the rapid production (within ten minutes) of lactic acid in the oral cavity. In their experiments they find a marked increase in the lactic acid content of the oral cavity within ten minutes after the complete solution of tablets of dextrose, sucrose or starch in the mouth. Control experiments by these workers demonstrate that this rapid production of lactic acid in the oral cavity can be ascribed to the activity of oral micro-organisms.

Thus, for the first time there now is not only a demonstration of the production of acids in the oral cavity but also a demonstration of the production of a definite acid—lactic acid.

J. LEWIS BLASS, Ph.G., D.D.S.,  
New York University College of Dentistry.

### A LESSON IN PSYCHOSOMATIC RELATIONSHIPS

To the Editor:—In a recent issue of the *American Journal of the Medical Sciences* (199:539 [April] 1940) there is a report by C. H. Brown on the role of foci of infection in the pathogenesis of arthritis entitled "Foci of Infection in Psychiatric Patients." The author compared the incidence of such foci in a group of arthritic patients with the incidence of foci of infection in a group of "healthy" controls. He found that there was no essential difference in the incidence of foci of infection in the two groups and drew the conclusion, therefore, that foci of infection did not constitute a sufficient factor in the pathogenesis of arthritis and that another factor was necessarily involved, such as a constitutional hereditary predisposition to arthritis or a state of allergy to the bacteria in the foci. This conclusion appears valid and logical enough until one considers his so-called "healthy" controls.

I quote from Dr. Brown's paper: "It is the purpose of the present study to determine the incidence of foci of infection in a group of patients who are apparently physically well. The group of patients we selected to study are a group of psychotic patients who were hospitalized because of mental rather than physical sickness. There is no reason to expect in a group of mentally sick, but apparently physically well patients, any difference in incidence of foci of infection than would obtain in a similar economic and geographic group of physically normal human beings." Brown thus bases his selection of cases on a rather crude dualistic conception of mind-body relationship, i. e. disease is either "mental" or "physical." The fallacy arising from such a point of view is interesting.

In a study on the incidence of arthritis in a group of more than 15,000 psychotic patients Gregg (*The Paucity of Arthritis Among Psychotic Cases*, *Am. J. Psychiat.* 95:853 [Jan.] 1939) discovered that disabling arthritis occurred seventeen times more frequently in the community at large than among psychotic patients in Massachusetts state hospitals. He presents other data in his paper supporting the general thesis that psychotic patients are strangely immune to arthritis.

It is not my purpose in this communication to discuss the possible reasons for this interesting psychosomatic relationship. It is altogether conceivable, for example, that foci of infection do act as direct, self-sufficient, etiologic agents in the pathogenesis of arthritis but that the psychotic process sets certain other factors into motion which protect the joints from arthritis. Suffice it to say that a group of psychotic patients do not constitute "normal" physical controls.

LOUIS LINX, M.D., Trenton, N. J.

## Medical Examinations and Licensure

### COMING EXAMINATIONS

#### NATIONAL BOARD OF MEDICAL EXAMINERS EXAMINING BOARDS IN SPECIALTIES

Examinations of the National Board of Medical Examiners and Examining Boards in Specialties were published in THE JOURNAL, December 28, page 2303.

#### BOARDS OF MEDICAL EXAMINERS

**ALABAMA:** Montgomery, June 17-19. Sec., Dr. J. N. Baker, 519 Dexter Ave., Montgomery.

**ARIZONA:** \* Phoenix, Jan. 7. Sec., Dr. J. H. Patterson, 826 Security Bldg., Phoenix.

**ARKANSAS:** \* Eclectic, Little Rock, June 5-6. Sec., Dr. Clarence H. Young, 1415 Main St., Little Rock.

**CALIFORNIA:** *Oral examination* (required when reciprocity application is based on a state certificate or license issued ten or more years before filing application in California), Los Angeles, Jan. 29. *Written*, Los Angeles, Feb. 24-27. Sec., Dr. Charles B. Pinkham, 1020 N St., Sacramento.

**COLORADO:** \* Denver, Jan. 7-10. Applications must be on file not later than Dec. 23. Sec., Dr. Harvey W. Snyder, 831 Republic Bldg., Denver.

**CONNECTICUT:** \* *Medical. Written*, Hartford, March 11-12. *Endorsement*, Hartford, March 25. Sec., Dr. Thomas P. Murdock, 147 W. Main St., Meriden. *Homoeopathic*, Derby, March 11-12. Sec., Dr. Joseph H. Evans, 1488 Chapel St., New Haven.

**DELAWARE:** July 8-10. Sec., Medical Council of Delaware, Dr. Joseph S. McDaniel, 229 S. State St., Dover.

**DISTRICT OF COLUMBIA:** \* Washington, May 12-13. Sec., Commission on Licensure, Dr. George C. Ruhland, 203 District Bldg., Washington.

**FLORIDA:** \* Jacksonville, June 23-24. Sec., Dr. William M. Rowlett, Box 786, Tampa.

**GEORGIA:** Atlanta, June. Sec., State Examining Boards, Mr. R. C. Coleman, 111 State Capitol, Atlanta.

**HAWAII:** Honolulu, Jan. 8-11. Sec., Dr. James A. Morgan, 48 Young Building, Honolulu.

**IDaho:** Boise, April 1. Dir., Bureau of Occupational License, Mr. H. B. Whittlesey, 335 State Capitol Bldg., Boise.

**ILLINOIS:** \* *Written*, Chicago, Jan. 21-22. *Reciprocity*, Chicago, Jan. 23. Supt. of Registration, Dept. of Registration and Education, Mr. Lucien A. File, Springfield.

**INDIANA:** Indianapolis, June 17-19. Sec., Board of Medical Registration and Examination, Dr. J. W. Bowers, Citizens Trust Bldg., Fort Wayne.

**MAINE:** Portland, March 11-12. Sec., Board of Registration of Medicine, Dr. Adam P. Leighton, 192 State St., Portland.

**MASSACHUSETTS:** Boston, March 11-13. Sec., Board of Registration in Medicine, Dr. Stephen Rushmore, 413-F State House, Boston.

**MICHIGAN:** \* Ann Arbor and Detroit, June 11-13. Sec., Board of Registration in Medicine, Dr. J. Earl McIntyre, 202-4 Hollister Bldg., Lansing.

**MINNESOTA:** \* Minneapolis, Jan. 21-23. Sec., Dr. Julian F. Du Bois, 350 St. Peter St., St. Paul.

**MONTANA:** *Reciprocity*, Helena, March 31. *Written*, Helena, April 1. Sec., Dr. S. A. Cooney, 216 Power Block, Helena.

**NEVADA:** *Reciprocity with oral examination*, Feb. 3. Sec., Dr. Fred M. Anderson, 215 N. Carson St., Carson City.

**NEW HAMPSHIRE:** Concord, March 13-14. Sec., Board of Registration in Medicine, Dr. T. P. Burroughs, State House, Concord.

**NEW JERSEY:** Trenton, June 17-18. Sec., Dr. Earl S. Hallinger, 28 W. State St., Trenton.

**NEW MEXICO:** Santa Fe, April 14-15. Sec., Dr. Le Grand Ward, 135 Sena Plaza, Santa Fe.

**NEW YORK:** Albany, Buffalo, New York and Syracuse, Jan. 27-30. Chief, Bureau of Professional Examinations, Mr. Herbert J. Hamilton, State Education Department, 315 Education Bldg., Albany.

**NORTH DAKOTA:** Grand Forks, Jan. 7-10. Sec., Dr. G. M. Williamson, 4½ S. Third St., Grand Forks.

**OREGON:** \* Portland, Jan. 14-16. Exec. Sec., Miss Lorraine M. Conlee, 608 Failing Bldg., Portland.

**PENNSYLVANIA:** Philadelphia, January 7-11. Acting Sec., Bureau of Professional Licensing, Miss Marguerite G. Steiner, 358 Education Bldg., Harrisburg.

**SOUTH DAKOTA:** \* Pierre, Jan. 21-22. Dir., Medical Licensure, Dr. J. F. D. Cook, Pierre.

**VERMONT:** Burlington, Feb. 11. Sec., Dr. W. Scott Nay, Underhill.

**WASHINGTON:** \* Seattle, Jan. 13-15. Sec., Department of Licenses, Mr. Nelson N. Vaughan, Olympia.

**WEST VIRGINIA:** Charleston, March 3. Sec., Public Health Council, Dr. Arthur E. McClue, State Capitol, Charleston.

**WISCONSIN:** \* Madison, Jan. 14-16. Applications must be on file not later than Jan. 2. Sec., Dr. H. W. Shutter, 425 E. Wisconsin Ave., Milwaukee.

**WYOMING:** Cheyenne, Feb. 3-4. Sec., Dr. M. C. Keith, Capitol Bldg., Cheyenne.

\* Basic Science Certificate required.

#### BOARDS OF EXAMINERS IN THE BASIC SCIENCES

**CONNECTICUT:** Feb. 8. Address State Board of Healing Arts, 1945 Yale Station, New Haven.

**DISTRICT OF COLUMBIA:** Washington, April 21-22. Sec., Commission on Licensure, Dr. George C. Ruhland, 203 District Bldg., Washington.

**FLORIDA:** De Land, June 7. Applications must be on file not later than May 24. Sec., Prof. J. F. Conn, John B. Stetson University, De Land.

**IOWA:** Des Moines, Jan. 14. Dir., Division of Licensure and Registration, Mr. H. W. Greife, Capitol Bldg., Des Moines.

**MICHIGAN:** Ann Arbor, Detroit and East Lansing, Feb. 14-15. Sec., Miss Flora E. Dube, East Lansing.

**MINNESOTA:** Minneapolis, Jan. 7-8. Sec., Dr. J. Charnley McKinley, University of Minnesota, 126 Millard Hall, Minneapolis.

**NEBRASKA:** Omaha, Jan. 14-15. Dir., Bureau of Examining Boards, Mrs. Clark Perkins, 1009 State Capitol Bldg., Lincoln.

**OREGON:** Portland, Feb. 15. Sec., State Board of Higher Education, Mr. Charles D. Byrne, University of Oregon, Eugene.

**RHODE ISLAND:** Providence, Feb. 19. Sec., Division of Examiners, Rev. Nicholas H. Serror, Providence College, Providence.

**WASHINGTON:** Seattle, Jan. 9-10. Sec., Department of Licenses, Mr. Nelson N. Vaughan, Olympia.

### Nevada May Report

Dr. Frederick M. Anderson, secretary, Nevada State Board of Medical Examiners, reports the written examination for medical licensure held at Carson City, May 6, 1940. The examination covered 14 subjects and included 80 questions. An average of 75 per cent was required to pass. Three candidates were examined, all of whom passed. The following schools were represented:

School	PASSED	Year Grad.	Per Cent
College of Medical Evangelists.....	(1940)		84.4
Harvard Medical School.....	(1934)		87.3
St. Louis University School of Medicine.....	(1926)		75.7

Five physicians were licensed to practice medicine by reciprocity on May 6 and August 5. The following schools were represented:

School	LICENSED BY RECIPROCITY	Year Grad.	Reciprocity with
University of California Medical School.....	(1922)		California
University of Colorado School of Medicine.....	(1938)		Utah
University of Nebraska College of Medicine.....	(1939)		Nebraska
University of Western Ontario Medical School.....	(1924)		Ohio
McGill University Faculty of Medicine.....	(1937)		California

### California July Report

Dr. Charles B. Pinkham, secretary, California State Board of Medical Examiners, reports the written examination for medical licensure held at Los Angeles, July 16-18, 1940. The examination covered 9 subjects and included 90 questions. An average of 75 per cent was required to pass. One hundred and twenty-eight candidates were examined, 111 of whom passed and 17 failed. The following schools were represented:

School	PASSED	Year Grad.	Per Cent
University of Arkansas School of Medicine.....	(1938)		75.9
College of Medical Evangelists.....	(1940)		76.7,
76.7, 77.7, 77.7, 79.1, 79.7, 80.3, 80.4, 80.9, 81.3,			
81.6, 81.9, 82.6, 83, 83.2, 83.4, 83.7, 83.9, 84.1, 84.2,			
84.8, 85, 85.1, 85.3, 85.7, 85.9, 85.9, 86.1, 86.2,			
86.2, 86.8, 86.8, 87.6, 88.1, 90.8			
Stanford University School of Medicine... (1940)	82.6, 86.2, 86.9, 88.6		
University of California Medical School..... (1940)	81.3, 82.3,		
83.6, 85.4, 86.9, 87.1			
University of Southern California School of Medicine..... (1940)	76.3,		
76.7, 77.1, 78.3, 79.1, 79.2, 79.4, 80.8, 81, 82.3,			
82.6, 82.8, 82.9, 82.9, 83.4, 83.8, 84, 84.8, 85.1, 85.4,			
85.4, 86.4, 88.3			
Loyola University School of Medicine..... (1940)	75.2, 80.9, 82.2		
Northwestern University Medical School..... (1940)	78.8,* 82.6		
The School of Medicine of the Division of the Biological Sciences.....	(1938)		81.9
University of Illinois College of Medicine.....	(1940)		86.3
University of Michigan Medical School.....	(1939)		83.7
Wayne University College of Medicine.....	(1940)		87.9
University of Minnesota Medical School..... (1940)	79.7, 83.1		83.3
St. Louis University School of Medicine.....	(1940)		83.2
Creighton University School of Medicine.....	(1939)		83.1
Columbia University College of Physicians and Surgeons.....	(1939)		84.3
New York Medical College, Flower and Fifth Avenue Hospitals.....	(1939)		85.4
New York University College of Medicine.....	(1940)		90.4
Syracuse University College of Medicine.....	(1940)		79.2
University of Oklahoma School of Medicine.....	(1939)		86.8
University of Oregon Medical School.....	(1939)		83.4
Temple University School of Medicine.....	(1940)		80.7
University of Pennsylvania School of Medicine.....	(1939)		76.3
University of Texas School of Medicine.....	(1937)		80.9
Marquette University School of Medicine.....	(1940)		80
University of Wisconsin Medical School.....	(1939)		79.2
University of Toronto Faculty of Medicine.....	(1936)		82.7
McGill University Faculty of Medicine.....	(1934)		87.7
Leopold-Franzens-Universität Medizinische Fakultät, Innsbruck.....	(1926)		86.9
Medizinische Fakultät der Universität Wien.....	(1913)		90.3,
(1920) 79, (1937) 85.2			
Universita Karlova Fakulta Lékařská, Praha.....	(1926)		78.9
Université de Paris Faculté de Médecine.....	(1932)		81
Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin.....	(1927) 77.8, (1934)		81.7
Johann Wolfgang Goethe-Universität Medizinische Fakultät, Frankfurt-am-Main.....	(1930)		81
Ludwig-Maximilians-Universität Medizinische Fakultät, München.....	(1922) 81.4, (1931)		77.8
Rheinische-Friedrich-Wilhelms-Universität Medizinische Fakultät, Bonn.....	(1918)		75.2
School	FAILED	Year Grad.	Number Failed
College of Medical Evangelists.....	(1939)		1
Stanford University School of Medicine.....	(1940)		1
University of California Medical School.....	(1940)		1
University of Southern California School of Medicine.....	(1940)		1
Loyola University School of Medicine.....	(1940)		1
State University of Iowa College of Medicine.....	(1939)		1
Boston University School of Medicine.....	(1933)		1
St. Louis University School of Medicine.....	(1940)		1
McGill University Faculty of Medicine.....	(1940)		1

Deutsche Universität Medizinische Fakultät, Prag.....	(1923)	1
Johann Wolfgang Goethe-Universität Medizinische Fakultät, Frankfurt-am-Main .....	(1922)	1
Julius-Maximilians-Universität Medizinische Fakultät, Würzburg .....	(1923)	1
Rheinische Friedrich-Wilhelms-Universität Medizinische Fakultät, Bonn .....	(1927)	1
Universität Heidelberg Medizinische Fakultät.....	(1927)	1
Latvijas Universitāte Medicīnas Fakultāte, Rīga.....	(1928)	1
Unwersytet Stefana Batoro Wyzdział Lekarski, Wilno.....	(1937)	1
Universidade de Lisboa Faculdade de Medicina.....	(1938)	1

\* This applicant has received the M.B. degree and will receive the M.D. degree on completion of internship.

## Bureau of Legal Medicine and Legislation

### MEDICOLEGAL ABSTRACTS

**Malpractice: Limitation of Actions; Accrual of Right of Action.**—The defendant physician performed a surgical operation on the plaintiff's gallbladder in 1923. After the operation and during the period of convalescence he informed the plaintiff that "he had punctured every cell in her gallbladder and that her gallbladder was clean now and that she need not worry any more." Some time thereafter the plaintiff moved to another state and never again consulted the defendant. In October 1937 she consulted other physicians who discovered, by means of roentgenograms, that a gauze sponge had been left in her body. In 1938, within one year after the discovery of the sponge, she brought suit against the defendant for malpractice. She alleged that the defendant's failure to remove the sponge had caused her gallbladder to become infected, which resulted in many complications, internal ailments and great physical pain and disability, necessitating expensive medical and hospital care. From a judgment in favor of the physician the plaintiff appealed to the Supreme Court of Alabama.

The Alabama statute of limitations in tort cases is one year and in contract cases six years. The defendant contended that the plaintiff's action was barred by the statute of limitations, since it was not brought until fifteen years after the operation. The plaintiff, however, claimed that the operation fifteen years before had never been completed because a foreign substance, which the defendant was under obligation to discover and remove, had been left in her body. She contended, therefore, that the statute of limitations did not begin to run until that foreign substance was discovered, and so her suit was not barred, since she had instituted it within one year after discovery. But, said the Supreme Court, the decisions are practically unanimous in holding that, in the absence of a fraudulent concealment, the statute of limitations begins to run when the relation of physician and patient ends with reference to the ailment treated. It is true that when confidential relations exist, as between a physician and his patient, the duty to disclose may render silence fraudulent, but knowledge of the facts is a necessary element of fraudulent concealment. In the present case, although the plaintiff alleged that the defendant, in informing her that "her gallbladder was clean now," had made a misrepresentation of fact when he either knew that his statement was false or did not know that it was true, at no time did she allege or prove that he knew that he had left the sponge in her body. In fact, whether the statement credited to the defendant was more than merely a reassuring professional opinion, and understood as such, is questionable. The court was of the opinion that, in the absence of proof of actual knowledge on the part of the defendant that he had left the sponge in the operative wound, there was no fraudulent concealment. Since the plaintiff did not return to the defendant for further treatment after she left the state, the defendant was not responsible for the failure of other physicians to utilize the roentgen ray more promptly to discover the presence of the foreign substance in her body. Certainly, what the defendant said to the plaintiff at the time of the operation did not in any way prevent or delay the discovery of the sponge by other physicians, since there was no evidence that they relied on the defendant's statement. Accordingly, the Supreme Court held that the action was barred by the statute of limitations and so affirmed judgment in favor of defendant.—*Hudson v. Moore*, 194 So. 147 (Ala. 1940).

**Hospitals: Liability for Death of Patient Allegedly Due to Exposure to Draft.**—In January 1937 the automobile in which the plaintiff's son was riding struck a telephone pole and plunged into a lake. He was removed from the ice-cold water and rushed to the defendant clinic. When he arrived at the clinic he was unconscious, cold and in a severe state of shock. Emergency treatment was provided on a sunporch and an attendant then moved him into a room and placed him on a cot directly between an open window and the door in such a position that a continual draft blew over him. He was not kept well covered and only one small hot water bottle was placed at his feet. A physician ordered a pneumonia jacket placed on him but the nurse failed to do so. Before he died he vomited such a large quantity of muddy water that it overflowed an emesis basin and wetted the bed clothes, which were not changed. He died two days after admission to the clinic. According to the death certificate, the cause of death was "Pulmonary edema and circulatory failure due to injury and inhalation of muddy water into lungs." The plaintiff, individually and as administratrix of her son's estate, sued the defendant clinic to recover damages for the death of her son, which she alleged had been caused by the negligent treatment rendered. The defendant's evidence tended to show that the care and treatment furnished by its staff was in accordance with approved methods. The trial court granted the defendant's motion for judgment notwithstanding the verdict for the plaintiff and dismissed the suit. The plaintiff then appealed to the Supreme Court of Washington.

The plaintiff contended that the defendant was negligent in placing her son, only partially covered, on a cot in front of an open window so that he caught pneumonia and that that was the real cause of his death. But, as the Supreme Court pointed out, the question for determination was whether or not the most probable cause of death was the defendant's failure properly to treat the deceased. It is a well settled rule of law, said the court, that where the evidence goes no further than to show that death may have resulted from one of several causes for which there is liability and from another or other causes as to which there is no liability, then the jury cannot speculate or conjecture between the several causes and return a verdict based on a cause for which there is liability. In view of the "desperate state" of the deceased when he was taken to the clinic, the court believed that it was impossible for reasonable minds to conclude that it was more probable that he died as the result of the defendant's treatment than from the lengthy exposure in freezing water following the accident, or to conclude that there was a greater probability that death would not have resulted but for the lack of proper treatment. The judgment for the defendant was therefore affirmed.—*Nelson v. Columbia Clinic, Inc.*, 96 P. (2d) 575 (Wash. 1940).

## Society Proceedings

### COMING MEETINGS

- Annual Congress on Industrial Health, Chicago, Jan. 13-15. Dr. Carl M. Peterson, 535 N. Dearborn St., Chicago, Secretary.
- Annual Congress on Medical Education and Licensure, Chicago, Feb. 17-18. Dr. W. D. Cutter, 535 North Dearborn St., Chicago, Secretary.
- American Orthopsychiatric Association, New York, Feb. 20-22. Dr. Norville C. La Mar, 149 East 73d Street, New York, Secretary.
- Central Surgical Association, Ann Arbor, Mich., Feb. 28-March 1. Dr. George M. Curtis, Ohio State University, Columbus, Ohio, Secretary.
- Eastern Section, American Laryngological, Rhinological and Otolological Society, Philadelphia, Jan. 10. Dr. N. S. Weinberger, Robert Packer Hospital, Sayre, Pa., Chairman.
- Middle Section, American Laryngological, Rhinological and Otolological Society, Chicago, Jan. 27. Dr. Walter H. Theobald, 307 North Michigan Blvd., Chicago, Chairman.
- Pacific Coast Surgical Association, Los Angeles, Feb. 19-22. Dr. H. Glenn Bell, University of California Hospital, San Francisco, Secretary.
- Society of Surgeons of New Jersey, Newark, Jan. 29. Dr. Walter B. Mount, 21 Plymouth St., Montclair, Secretary.
- Society of University Surgeons, St. Louis, Feb. 14-15. Dr. Frank Glenn, 525 East 68th St., New York, Secretary.
- Southern Section, American Laryngological, Rhinological and Otolological Society, Nashville, Tenn., Jan. 8. Dr. William G. Kennon, Doctors Bldg., Nashville, Tenn., Chairman.
- Western Section, American Laryngological, Rhinological and Otolological Society, San Francisco, Feb. 1-2. Dr. Robert C. Martin, 384 Post St., San Francisco, Chairman.

## Current Medical Literature

### AMERICAN

The Association library lends periodicals to members of the Association and to individual subscribers in continental United States and Canada for a period of three days. Three journals may be borrowed at a time. Periodicals are available from 1930 to date. Requests for issues of earlier date cannot be filled. Requests should be accompanied by stamps to cover postage (6 cents if one and 18 cents if three periodicals are requested). Periodicals published by the American Medical Association are not available for lending but can be supplied on purchase order. Reprints as a rule are the property of authors and can be obtained for permanent possession only from them.

Titles marked with an asterisk (\*) are abstracted below.

#### American Journal of Ophthalmology, St. Louis

23:1199-1310 (Nov.) 1940

- Pharmacologic Behavior of Intra-Ocular Muscles: I. Problem of Sensitization and Methods for Its Study. E. Sachs and P. Heath, Detroit.—p. 1199.
- Passage of Horse Serum from Blood Stream into Aqueous Humor of Normal and Immunized Animals. L. Guy, New York.—p. 1209.
- Cultivation of Conjunctivitis-Producing and Keratitis-Producing Agents on Chorioallantoic Membrane of Chick Embryo. P. Thygeson, New York.—p. 1217.
- Glass Membranes in Eye: Part I. Bowman's Membrane, Descemet's Membrane and Lens Capsule. A. Loewenstein, Glasgow, Scotland.—p. 1229.
- Practical Skiascopy. E. Jackson, Denver.—p. 1239.
- General Hypertension and Peripheral Optic Pathways. J. Igersheimer, Istanbul, Turkey.—p. 1243.
- Subjective "Lightning Flashes." R. F. Moore, London, England.—p. 1255.
- Selection of Test Object in Perimetry. O. P. Bourbon, Los Angeles.—p. 1260.

#### American Journal of Surgery, New York

50:225-446 (Nov.) 1940. Partial Index

- Trigeminal Neuralgia with Demonstrable Gross Causative Lesions: Report of Five Cases. R. B. Raney and A. A. Raney, Los Angeles.—p. 227.
- Epiphyseal Changes Resulting from Acute Infections of Bone. H. B. Macey, Rochester, Minn.—p. 239.
- Ureterocoele: Treatment by Transurethral Resection. P. S. Adams, Omaha.—p. 249.
- \*Treatment of Furuncles, Carbuncles and Abscesses of Staphylococcal Origin with Thiazole Derivatives of Sulfanilamide. C. A. Beling, South Orange, N. J., and A. R. Abel, East Orange, N. J.—p. 258.
- Failures in Rhinoplastic Surgery: Causes and Prevention. J. Safian, New York.—p. 274.
- Suction Operation for Total Removal of Cataract: Report of 228 Consecutive Cases. M. J. Blaess, Detroit.—p. 288.
- Postoperative Pulmonary Complications: Analysis of Etiology, Diagnosis, Prophylaxis and Treatment. E. J. Gordon, Washington, D. C.—p. 294.
- Immediate Restoration of Active Extension of Knee Following Flexion Deformities. R. L. Preston, New York.—p. 303.
- Unexpected Occurrence of Sugar in Urine Following Glucose Infusions. R. A. Cutting, Washington, D. C.—p. 306.
- Practical Application of the Falling Drop Method for Determining Surgical Prognosis: Preliminary Report. M. N. Foote and G. R. Gerst, Brooklyn.—p. 316.
- New Treatment for Sloughing Wounds: Preliminary Report. S. T. Glasser, New York.—p. 320.
- Causes for Failure in Thoracoplasty. F. Bortone, Jersey City, N. J.—p. 327.
- \*Rare Malformation of Arm: Double Humerus with Three Hands and Sixteen Fingers. H. C. Stein and E. H. Bettmann, White Plains, N. Y.—p. 336.
- \*Bilateral Complete Syndactylism of All Fingers. S. L. Haas, San Francisco.—p. 363.

**Sulfanilamide Derivatives for Furuncles, Carbuncles and Abscesses.**—Beling and Abel used sulfamethylthiazole in 25 and sulfathiazole in 15 consecutive cases of staphylococcal infections; 13 of the cases were carbuncles, 12 furuncles and 15 abscesses. Staphylococci were cultured from the lesions of each patient and were recovered from the blood stream of 1. Thirty-eight of the patients were definitely improved after receiving a considerable quantity of the drug; 1 result was questionable because of the prolonged course of the disease and concomitant administration of staphylococcus vaccine. Furuncles were affected most readily and disappeared within four days, except in 2 instances; 1 had about ten furuncles and responded satisfactorily although eight days elapsed before the last one disappeared and the other patient, the one who had received the vaccine, was not definitely improved. Response to thiazole therapy depends in part on the developmental stage of the lesion when the drug is commenced. The earlier furuncles responded about 25 per cent more slowly than well developed lesions but receded without formation of pus. The latter

quickly soften, discharge their contents promptly and heal. No core forms and the discharge is liquid. The induration and redness around the lesion disappear rapidly. Carbuncles responded more slowly because of the extensive nature of the lesion but did so with relative rapidity and in essentially the same manner. The surrounding infiltrated areas became soft and the redness disappeared, while the drainage assumed the character described for furuncles. Any cores formed prior to treatment were soft and easily dislodged. Diabetes mellitus is not a contraindication to treatment. It may prolong the time required for the lesion to improve, but this is not always true as the carbuncle of one such patient responded in six days. If it is deemed necessary to excise a carbuncle, the authors advise giving sulfathiazole for twenty-four hours prior to excision, as they believe that this will tend to prevent spread of infection, the development of septicemia and residual local infection. Abscesses usually responded to treatment in from five to eight days, depending on their stage before treatment and on the presence of cellulitis. The authors state that, if staphylococcal cellulitis is treated before there is any tendency to localization, resolution may take place without formation of pus. If pus does form, the abscess will be insignificant. When an abscess has already begun to form, the time taken to clear up the cellulitis and the abscess together is usually several days longer. One case with cellulitis and abscesses cleared in twelve days, 1 with multiple intractable abscesses throughout both breasts cleared up within five days and in another case there was no effect from sulfamethylthiazole. In the last mentioned case there were honeycombed abscesses throughout the scalp and subaponeurotic region following an injury to the scalp and extensive cellulitis; also diabetes was present. Chemotherapy alone is not sufficient treatment for abscesses or any other collection of pus that is accessible. These various lesions should be handled in the customary manner with the addition of thiazole medication by a suitable route.

**Double Humerus with Three Hands and Sixteen Fingers.**—Stein and Bettmann observed a woman of 52 presenting a normal left arm, and a right arm double average size and terminating in three hands with sixteen fingers of more or less normal appearance. The fact that the patient manifested no other abnormalities or defects and that none have been discovered in her family apparently excludes an endogenous (hereditary) factor. Some type of damage originating from without during gestation is a more probable cause. The authors attempt to explain the anomaly as follows: Nonspecific irritation may have occurred at a period of gestation when the right shoulder and arm were being formed but were not completely differentiated. Possibly an excessive amount of building material was present, and when the rate of growth was accelerated to make up for the harm done a double humerus and plural hands resulted. Some form of injury is thus the most probable explanation. The irritating mechanism could have been abnormally increased intra-abdominal pressure in pregnancy causing adhesions between the amnion and an extremity of the embryo; disease of the amnion or of the uterine mucosa; physical or mental trauma, infectious and toxic influences, maternal genital disease and the like, and alteration in milieu as demonstrated by various animal experimenters. The authors believe that, whatever pathogenic factor is postulated, the spina bifida of the fifth cervical vertebra was presumably the result of an insufficient vertebral segment or a secondary injury to the area of the somites. They believe that the causative injury took place early in embryonic life, probably in the third or fourth week. Fracture of the scapula-arm-hand blastema in the third or fourth week may have caused a process of degeneration, followed perhaps by a process of super-regeneration with rearrangement of the skeleton. Perhaps as a result of this rearrangement the additional ulna materialized and the olecranon was rotated in the ventral plane. The patient feels in no way inhibited by her deformity (except for her shyness). She has been a telephone operator and file clerk for twenty-five years with little inconvenience. She has refused any attempts at correction.



**Bilateral Complete Syndactylism of All Fingers.**—Haas presents complete bilateral syndactylism in a brother and a sister. Their mother had had severe syndactylism of both hands. These deformities are of congenital origin and represent a regressive atavistic trait. Restoration of six fingers with their corresponding metacarpals was secured on both of the boy's hands. He is able to do many things with either hand that he could not do before operation. The treatment consisted of a series of six plastic operations over a period of nine months. Sufficient time was allowed between the operations to allow the infant to recuperate and also to attain the full effect of each operative procedure. The six fingers are going to remain for about a year, and when it is determined which is least useful it will be sacrificed. Since this paper has been submitted for publication, similar operations have been performed on the sister, restoring five fingers on both hands.

## American Review of Tuberculosis, New York

42:551-697 (Nov.) 1940

**Tuberculin Reactors and Exposure Cases: Follow-Up Study of Cases Removed from Contact: Inquiry into Endogenous Reinfection.** J. A. Johnston, P. J. Howard, F. J. Smith and B. H. Douglas, Detroit.—p. 551.

**Immobilization of Lungs Through Pressure: Development of Method of Equalizing Pressure on Both Sides of Chest Wall with Maintenance of Adequate Pulmonary Ventilation.** A. L. Barach, with technical assistance of M. Eckman, New York.—p. 586.

**\*Monaldi's Suction Aspiration of Tuberculous Cavities.** E. Kupka and E. S. Bennett, Olive View, Calif.—p. 614.

**Bronchial Obstruction and Collapse Therapy.** A. H. Aufses, New York.—p. 622.

**Thoracoplasty in Fifth and Sixth Decades.** R. Shapiro and C. W. Munz, Springfield, Ohio.—p. 631.

**Thoracoplasty Following Pneumothorax: Dangers and Results.** I. L. Cutler, Rutland, Mass.—p. 640.

**Tuberculosis—An Intimate Chronicle.** J. A. O'Hale, Brooklyn.—p. 644.

**\*BCG Vaccine: Its Preparation and Local Reaction to Its Injection.** J. D. Aronson, Philadelphia; Erma I. Parr and R. M. Saylor.—p. 651.

**Vitamin C in Pulmonary Tuberculosis.** A. Kaplan and Marian E. Zonnis, St. Louis.—p. 667.

**Vocational Rehabilitation of the Tuberculous: Preliminary Report.** Grace H. Carlson and D. H. Dabelstein, Oak Terrace, Minn.—p. 674.

### Monaldi's Suction Aspiration of Tuberculous Cavities.

—Kupka and Bennett have attempted the puncture of cavities in 22 cases; they failed to locate the cavity with the exploratory needle in 3, and no attempt to introduce the trocar was made. They succeeded in 2 with the needle, but failed to reach the cavity with the trocar, leaving 17 in which the catheter was introduced into the cavity and suction was applied. Ten of these patients are still under suction treatment and therefore only tentative statements can be made. Pleural symphysis was present in 11 patients and pleural space obliteration was produced in 6 by giving one or more autotransfusions. Four had slight hemoptysis at the time of puncture. Four developed mild infection of the thoracic wall; all of these subsided. Two patients died. Among the remaining 15, suction has been discontinued in 5. The cavity has closed and the sputum has become negative for six months in 1. In the second patient the sputum has been converted and the cavity has almost closed, but later serial planigrams showed rapid increase in the size of the cavity necessitating a thoracoplasty. The cavity has closed and the sputum of the third patient has been converted. Now that the cavity is reopening, a thoracoplasty may be done. The patient's condition compared with the critical state at the time of puncture is now fairly good. In the fourth patient the cavity had been reduced to one third of its previous size, when the catheter was accidentally pulled out and could not be replaced. She had had a first stage thoracoplasty a year before and this was followed by a contralateral spread and a downhill course. Now the condition of the opposite lung, as well as her general condition, have so improved during suction aspiration that thoracoplasty can be completed. The fifth patient, with bilateral apical cavities, accidentally extruded her catheter, and puncture will be repeated. She showed no improvement after two months of treatment. Of the 10 patients still under suction treatment, the sputum has been converted in 6, and all but 1 have shown the marked diminution in the size of their cavities. In 3 the cavities are so small that planigrams show them barely visible around the tip of the catheter. Of the 4 who still have positive sputum, the cavities of 2 are markedly decreased and the

patients so improved that they have become good thoracoplasty risks. The remaining 2 patients had extremely large cavities; both are much improved but their ultimate fate is dubious; there is a possibility that they may yet become thoracoplasty risks. Of the entire series, 5 patients had two cavities at the time the larger one was punctured. The sputums of none of these have been converted, although the cavity secretions of 2 became negative. The authors believe that Monaldi's prolonged suction as an independent procedure under ideal conditions may bring about complete obliteration of cavities, that under less ideal conditions it may serve as a preparatory procedure for thoracoplasty, and that symptomatic relief may be afforded patients with giant cavities causing exhausting cough, choking attacks and severe toxemia. While its final place in therapeutics must await the test of time, the present results are encouraging.

**Tuberculosis Protection from BCG Vaccine.**—Aronson and his collaborators vaccinated from February 1936 to February 1938 1,565 Indian children from 1 to 19 years of age with BCG vaccine. During the same period 1,460 persons of the same age and sex, living in the same area and under the same conditions, were inoculated with 0.1 cc. of sterile physiologic solution of sodium chloride and served as controls. Before their inclusion in this study both groups failed to react to intracutaneous injection of 0.00002 and 0.005 mg. of purified protein derivative. Roentgenograms of the chests of most members of the two groups were taken either before or shortly after vaccination and at yearly intervals thereafter; also the members of both groups were retested with the same preparation of purified protein derivative. These Indians live under widely different climatic conditions (Arizona, Wyoming, North Dakota, South Dakota and Alaska) and are for the most part indigenous to their present locality. While their physical characteristics, dietary habits and social and economic patterns vary widely, their economic level is almost uniformly low. The BCG vaccine was injected intracutaneously over the deltoid region. It produced no untoward local or general reaction, and no instance of abscess formation or ulceration of the regional lymph nodes was noted. The local tissue response varied in different individuals. The relationship of the character of the local tissue reaction to resistance to tuberculosis is being studied. One year after vaccination, 93.3 per cent of 1,481 persons reacted to the intracutaneous injection of either 0.00002 or 0.005 mg. of purified protein derivative. Two years after vaccination 93.3 per cent of 1,446 persons retested were tuberculin positive and in three years 95.3 per cent of 619 persons reacted positively. The antigenicity appeared to be influenced by the rate of growth of the culture used in preparing the vaccine but not by the age of the culture or the number of generations that the culture had been grown on bile-free medium. Because of the marked variation in the results obtained by different investigators, the authors suggest that the preparation of BCG vaccine and the determination of the resulting allergy be made uniform. The BCG vaccine that they used was prepared in a field laboratory and was used within three days.

## Archives of Internal Medicine, Chicago

66:1011-1190 (Nov.) 1940

**\*Diabetes Mellitus and Syphilis: Study of 258 Cases.** L. T. McDaniel, Boston; H. H. Marks, New York, and E. P. Joslin, Boston.—p. 1011.

**Electrolyte Balance During Treatment, Crises and Severe Infection in Cases of Addison's Disease: Action of Adrenal Cortical Extracts.** J. A. Greene and G. W. Johnston, Iowa City.—p. 1052.

**\*Anatomic Foundation of Anacidty: Gastroscopic Study.** R. Schindler, P. B. Nutter, Chicago; H. E. Groom, Akron, Ohio, and W. L. Palmer, Chicago.—p. 1060.

**Influence of Thiamine on Blood Sugar Levels in Diabetic Patients.** R. E. Kaufman, New York.—p. 1079.

**Relation of Fatty Acids and Bile Salts to Formation of Gallstones.** R. E. Dolkart, Boston; Marie Lorenz, K. K. Jones and C. F. G. Brown, Chicago.—p. 1087.

**\*Syndrome of Subnormal Circulation in Ambulatory Patients.** I. Starr and L. Jonas, Philadelphia.—p. 1095.

**Syphilis: Review of Recent Literature.** C. F. Mohr, P. Padgett and J. E. Moore, Baltimore.—p. 1112.

**Diabetes Mellitus and Syphilis.**—McDaniel and his associates present an analysis of 258 cases of proved diabetes mellitus with syphilis. These patients were encountered among 15,095 diabetic patients, an incidence of 1.7 per cent. Certain specific criteria were fulfilled in each case, and no proof for



the diabetes as being due to the syphilis was found. The chief causes of diabetes (heredity, overweight and age at onset) were the same for diabetic patients with syphilis as for those without syphilis. The authors state that, if "syphilitic diabetes" occurs, theoretically it would most likely be a late manifestation of syphilis in older persons, except in patients with congenital syphilis, in whom diabetes is uncommon. Part of the evidence against the relationship of the two diseases is that of the 258 patients 188 were men and 70 women, a ratio of only 37.2 female to each hundred male patients. This is in great contrast to the ratio in whole series of diabetic patients from 1897 to 1933, in which there were 112.4 female per hundred male patients. This is a good point in indicating that syphilis has little to do with diabetes. Not a single instance of diabetes was cured by optimal antisiphilitic treatment. Usually neither does a patient with syphilis and diabetes have a type of diabetes different from that of the usual patient of the same age. The authors have not been able to recognize the characteristics of such a clinical entity as "syphilitic diabetes."

**Anatomic Foundation of Anacidity.**—Schindler and his co-workers made a gastrosopic study of 120 patients with histamine-proved anacidity; in 19 of these the anacidity was produced artificially. Gastrosopic examination revealed the following: 1. Gross anatomic lesions were present in all except 5 patients; in 1 anatomic changes invisible gastrosopically had to be assumed because of chronic bismuth poisoning and in 4 psychogenic functional anacidity seemed possible but was not proved. 2. Diffuse inflammation was present in 55 patients; 6 presented hypertrophic gastritis, 12 superficial gastritis, 7 superficial gastritis with transition into atrophic gastritis and 30 atrophic gastritis. The diffuse changes were usually located in the body of the stomach. Anacidity appeared to be the result of an inflammatory process. The apparent extent and severity of the process do not necessarily bear a relationship to the anacidity. 3. In 3 members of families in which pernicious anemia occurred, histamine-proved anacidity was associated with severe atrophic gastritis. This weakens the theory of the inborn constitutional character of anacidity, for the anacidity may be attributed to the gastritis. 4. Of 16 patients with pernicious anemia and anacidity, superficial gastritis or superficial plus atrophic gastritis was seen in 2, patchy or complete atrophic gastritis in 12 and the gastric mucosa appeared normal after liver therapy in only 2. 5. The observations in 23 patients with malignant gastric tumor and histamine-proved anacidity were in accord with the concept that atrophic gastritis plus anacidity may precede gastric carcinoma and that in many cases severe atrophic gastritis may be responsible for the anacidity. Gastrosopic examination of 3 patients failed to reveal pathologic changes in the gastric mucosa. 6. Eight patients with anacidity following a gastric operation had severe diffuse gastritis. No diffuse gastritis and no anacidity were found in 2 before operation, whereas after operation severe purulent acute gastritis and later chronic gastritis with anacidity developed. It seems that the anacidity following gastric operation may be due not only to the reflux of intestinal contents but also to postoperative gastritis. 7. Definite diffuse inflammatory changes were usually found in 11 patients having histamine-proved anacidity after roentgen irradiation. This ranged from mild transient superficial to constant atrophic gastritis. However, at two observations an apparently normal gastric mucosa was seen. This proves that mild organic lesions of the gastric mucosa, producing anacidity, may be present without showing pathologic changes gastrosopically.

**Subnormal Circulation in Ambulatory Patients.**—Starr and Jonas describe the signs and symptoms found in 100 ambulatory hospital patients who had subnormal basal or resting circulations estimated by their cardiac output. The syndrome is sufficiently definite to permit its diagnosis when methods of estimating cardiac output are not available. Forty-two of the patients were men and 58 women. The ages ranged between 50 and 59 years, but the incidence spread throughout adult life. When multiple diagnoses were possible the case was classified under the most important heading concerning circulation. Thus a case of diabetes with hypertension was classi-

fied only under the latter head; a case of angina pectoris with hypertension as the former. Of 30 patients with primary heart disease 18 had either recovered from cardiac infarcts or suffered from angina pectoris, 5 had rheumatic heart disease, 5 had heart block, 1 a calcified pericardium and 1 congenital heart disease. The next largest group consisted of 28 patients with hypertension, all having a systolic pressure in excess of 170 mm. of mercury, a diastolic pressure of more than 100 mm. or both. In a third group of 19 patients nothing abnormal was found. In 17 of them a diagnosis of functional heart disease or neurocirculatory asthenia was justified and the complaints of 2 were gastrointestinal. Of 11 patients with endocrine diseases 4 had diabetes, 4 had undergone partial thyroidectomies for hyperthyroidism, 2 were adjudged to have pituitary syndromes and 1 was a patient with Addison's disease. Of the remaining 12 patients 5 were elderly persons showing but little arteriosclerosis, 3 were convalescent from pneumonia, typhoid and catarrhal jaundice respectively, 4 each had migraine, malnutrition, postural hypotension or attacks suggesting atypical epilepsy with a cardiac lesion. Almost all (90 per cent) of the patients with subnormal circulation regarded themselves as unduly weak and easily fatigued; extreme weakness was the chief complaint of 17. Dyspnea on exertion was reported by 64 patients, and 19 took no exercise because of angina pectoris or peripheral vascular disease and so could not say whether they had undue dyspnea on exertion. The most characteristic symptom of the group was attacks of dizziness, present in 73 per cent. This occurred when the patients were upright, especially when they had just assumed that position. Light headedness, sometimes as attacks of faintness and sometimes just as "spells," was the major complaint of 26. Fourteen patients were subject to repeated attacks of fainting and 5 others had fainted once or twice. Forty of the patients considered themselves nervous; this was the major complaint of 8. The diagnoses were conversion hysteria, anxiety neurosis, neurasthenia and psychoneurosis. Many patients complained of frequent headaches of slight degree, 7 complained of cold extremities and 3 as suffering unduly from hot or cold weather. Physical examination adds little evidence to support the diagnosis of subnormal circulation, though weak or distant heart sounds in the absence of emphysema may excite suspicion. The pulse rate, the size of the heart and the basal metabolic rate are most frequently in the lower half of the normal range, but in some cases they are definitely subnormal. Ambulatory patients with subnormal circulation are common. The abnormality occurs in about half of the patients with coronary heart disease and less frequently in valvular heart disease. It is common in patients with hypertension whose hearts have not enlarged, in patients with so-called neurocirculatory asthenia, in patients with certain endocrine diseases and in convalescents from severe acute infections.

### Archives of Otolaryngology, Chicago

32:831-1006 (Nov.) 1940

- Tumors of External Auditory Canal: Report of Eleven Cases. H. E. Mitchell, Cleveland.—p. 831.  
Suppuration of Petrous Pyramid. R. L. Moorhead, Brooklyn.—p. 845.  
Penetration of Perinasal Tissues by Mercurochrome. A. H. Lawton and E. L. Ross, Chicago.—p. 853.  
\*Indurative or Myalgic Headache. E. M. Seydell, Wichita, Kan.—p. 860.  
Revision of Cerebellopontile Angle Lesion Syndrome, with Analysis of Vestibular Findings in Thirty-Four Cases of Verified Tumor of Cerebellopontile Angle. J. Winston, Philadelphia.—p. 877.  
Radiation Therapy for Carcinoma of Larynx: Observations After Twenty Years. S. Salinger, Chicago.—p. 887.  
Head Noises: Significance, Measurement and Importance in Diagnosis and Treatment. E. P. Fowler, New York.—p. 903.  
Complications of Surgical Treatment of Acute Mastoiditis. G. F. Harkness, Davenport, Iowa.—p. 915.  
Operative Treatment of Otosclerosis: Reply to a Recent Criticism. G. E. Shambaugh Jr., Chicago.—p. 927.  
Use of Anticoagulants in Cases of Postoperative Thrombosis and Embolism. F. W. Bancroft, New York.—p. 934.  
Use of Salt Pork in Cases of Hemorrhage. A. J. Cone, St. Louis.—p. 941.  
Purulent Otitis Media, Mastoiditis, Sinus Thrombosis and Suppuration of Petrous Pyramid. S. J. Kopecky, New York.—p. 962.

**Indurative or Myalgic Headache.**—Seydell describes indurative or myalgic headache, which he believes is frequently confused with disease of the accessory sinuses, migraine, otitis media and mastoiditis. The pain or headache is caused by myalgia of the neck. There may be spasm of one or more of

the cervical muscles, either with or without the appearance of nodules. The pain in the head results from a nodular or spastic condition of the muscles which occurs almost universally. In the majority of persons it is transient and mild, and little or no complaint is made. However, a patient may be so afflicted as to become a veritable invalid. The cause of the condition has not as yet been definitely established. The author is of the opinion that the following predisposing factors play a part: The patient's history usually presents evidence of vasomotor imbalance, allergy, hypersensitivity, high nervous tension or/and psychoneurosis. It is also probable that many have metabolic or endocrine disturbances, while others suffer from various forms of chronic arthritis. Occupation and environment are important factors; persons obliged to hold their heads in fixed positions for long periods are more subject to the complaint. Myalgia occurs almost exclusively in the postural muscles. The exciting factor for such headaches seems always to be an exposure to cold and drafts. The treatment consists of a definite type of massage and the injection of procaine hydrochloride into the painful areas in the neck.

### Canadian Public Health Journal, Toronto

31:457-514 (Oct.) 1940

- Public Health: Presidential Address. R. O. Davison, Regina, Sask.—p. 457.  
Commercialized Prostitution and Venereal Disease Control. D. H. Williams, Vancouver, B. C.—p. 461.  
World Health During 1939. J. J. Heagerty, Ottawa, Ont.—p. 473.  
Marriage and Mortality. F. G. Pedley, Montreal.—p. 477.  
Mental Hygiene and School Health Work. C. H. Gundry, Vancouver, B. C.—p. 482.

### Journal of Lab. and Clinical Medicine, St. Louis

26:287-442 (Nov.) 1940

- Tuberculosis—Present and Future. G. B. Webb, Colorado Springs, Colo.—p. 287.  
Dissecting Aneurysm of Aorta. A. Levitt, D. S. Levy and J. R. L. Cole, Buffalo.—p. 290.  
Note on *Saccharomyces Fragilis* Jorgensen Associated with Pathologic Conditions in Human Beings. N. C. Laffer, Tucson, Ariz.—p. 294.  
Action of Epinephrine Injected into Pericardial Sac. P. Blickensdorfer and J. A. Bone, Chicago.—p. 297.  
Torula Infection of Central Nervous System. L. H. Goldberg, Nyack, N. Y.—p. 299.  
Cutaneous Hypersensitivity to Iodine. J. L. Jacobs and A. Colmes, Boston.—p. 302.  
\*Acute Endocarditis Due to Anaerobic Pneumococcus. A. Hollander and Eva Landsberg, Brooklyn.—p. 307.  
Qualitative and Quantitative Study of Atmospheric Pollen at Moscow, Idaho. J. B. Daubenmire, Moscow, Idaho.—p. 311.  
Intramuscular Administration of Sodium Sulfapyridine. L. T. Hall, E. Thompson and R. J. Wyrns, Omaha.—p. 314.  
Giant Cell Tumor of Frontal Bone. J. J. Keegan and C. P. Baker, Omaha.—p. 319.  
Theory of Prophyryinogenesis. W. J. Turner, North Little Rock, Ark.—p. 323.  
Studies on Intravenous Injection of Colloids: II. Effects of Gum Acacia on Certain Functions of Liver with Notes on Its Effects on Production of Immune Bodies. W. K. Hall, New Orleans; R. B. Gibson and L. A. Weed, Iowa City.—p. 330.  
Blood Serum Magnesium in Bronchial Asthma and Its Treatment by Administration of Magnesium Sulfate. V. G. Haury, Philadelphia.—p. 340.  
Sodium and Potassium Studies in Persons With and Without Arterial Hypertension. D. W. Bennett, San Francisco.—p. 344.  
Effect of Iron on Phosphorus, Calcium and Nitrogen Metabolism. Adelaide P. Barer and W. M. Fowler, Iowa City.—p. 351.  
Alteration of Glucose Tolerance in Patients with Disease of Pituitary, Thyroid and Adrenal Glands by Changes of Diet. J. A. Greene and L. W. Swanson, Iowa City.—p. 360.  
Comparative Iodine Content of Whole Blood and Serum. K. P. Klassen, Ruth L. Bierbaum and G. M. Curtis, Columbus, Ohio.—p. 365.  
Comparative Studies on Absorption of Sulfanilamide. W. J. Siebert and F. Loose, St. Louis.—p. 371.

### Acute Endocarditis Due to Anaerobic Pneumococcus.

—Hollander and Landsberg report what they believe to be the first instance of the isolation of anaerobic pneumococci from the blood stream during life and also the first case of acute endocarditis caused by this organism. The onset with headache and swelling of the eye and the roentgen evidence of infection in the sinuses indicated that these were the primary foci, although not proved, as positive cultures were not obtained. As soluble sulfapyridine was not available then, intrathecal sulfanilamide was given and maintained at a blood level of 7.6 mg. per hundred cubic centimeters for five days.

Concurrently with the intrathecal sulfanilamide, oral sulfapyridine was instituted. After eleven days of treatment, despite a sulfapyridine blood level of 11.1 mg. a positive blood culture was obtained. For the next two days the temperature ranged between 99 and 101 F. After a further rise the intravenous therapy was discontinued. The patient continued to receive orally 60 grains (4 Gm.) of sulfapyridine daily. Nevertheless one week later the blood level was only 3.2 mg., at which time the patient became irrational and delirious. Convulsive seizures occurred, starting on the left side and becoming generalized in a few seconds. The course continued steadily downhill and the patient died. A lumbar puncture shortly before death showed a turbid fluid with innumerable gram-positive diplococci. On culture these organisms proved to be identical with those isolated from the blood. There was no relationship between the cultures and the blood concentration of sulfapyridine. Consent for necropsy was not given. The identity of the anaerobic pneumococcus was established by its solubility in bile, fermentation of inulin and quelling reaction with a homologous immune serum. Mice infected with mucin suspensions of these organisms were not protected by either sulfanilamide or sulfapyridine.

### Journal of Nervous and Mental Disease, New York

92:569-708 (Nov.) 1940

- Cerebral Arc of Corneal Reflex. A. E. Walker, Chicago.—p. 569.  
Constitutional Differences Between Deteriorated and Nondeteriorated Patients with Epilepsy: III. Dactylographic Studies. M. Brown and H. A. Paskind, Chicago.—p. 579.  
Note on Imagination and Its Exploitation: Psalmanazar and Hélène Smith. C. M. Campbell, Boston.—p. 605.  
Method for Shortening Duration of Lower Motor Neuron Paralysis by Cholinergic Facilitation. A. Wolf, New York.—p. 614.  
Cysticercus Cyst of Fourth Ventricle with Surgical Removal: Case Report. L. J. Adelstein, Los Angeles.—p. 623.  
Electric Corpus Changes and Reaction on Peripheral Nerves in Insulin Treated Schizophrenic Patients. M. Kastan, Cincinnati.—p. 630.  
Convulsion Seizures Following Eclampsia. H. G. Hadley, Washington, D. C.—p. 638.  
Mental and Neurologic Sequelae of Carbon Monoxide Asphyxia in Case Observed for Fifteen Years. Naomi Raskin and O. C. Mullaney, Boston.—p. 640.

### Journal of Neurophysiology, Springfield, Ill.

3:469-552 (Nov.) 1940

- Sensory Cortex of Chimpanzee. P. Bailey, J. G. Düsser de Barenne, H. W. Garol and W. S. McCulloch, New Haven, Conn.—p. 469.  
Unit for Sensory Reception in Cornea, with Notes on Nerve Impulses from Sclera, Iris and Lens. Sarah S. Tower, Philadelphia.—p. 486.  
Learning and Other Functions of Higher Nervous Centers of Sepia. F. K. Sanders and J. Z. Young, Oxford, England.—p. 501.  
Conversion of Phasic into Tonic Movements by Pyramid Lesions. F. A. Mettler and Cecilia C. Mettler, Augusta, Ga.—p. 527.  
Forebrain and Rage Reactions. E. A. Spiegel, H. R. Miller and M. J. Oppenheimer, New York.—p. 538.

### Laryngoscope, St. Louis

50:921-1024 (Oct.) 1940

- Disturbances of Function of Ear After Concussion of Brain. H. Brunner, Chicago.—p. 921.  
Panel Discussion: Infectious Lateral Sinus Thrombophlebitis. L. W. Dean, A. F. Hartmann, St. Louis; F. M. Law, New York; A. C. Furstenberg, Ann Arbor, Mich.; H. I. Lillie, Rochester, Minn.; I. Friesner, New York, and H. P. Mosher, Boston.—p. 950.  
\*Treatment of Sinusitis by Displacement Method: Report of 800 Cases Using Ephedrine, Neosynephrine, Bacterial Antigens and Foreign Proteins. L. K. Gundrum, Los Angeles.—p. 989.  
Nystagmus and Eye Deviations in Guinea Pigs with Lesions in Brain Stem. A. R. Buchanan, Denver.—p. 1002.  
The "Common Cold" and Common Sense. A. F. Holding, Albany, N. Y.—p. 1012.  
Tuberculosis: Assimilating Symptoms of Acute Ethmoid, Sphenoid Infection. H. M. Goodyear, Cincinnati.—p. 1019.

**Displacement Therapy in Sinusitis.**—Gundrum states that of the many treatments advocated for sinusitis he has had most success with the displacement treatment suggested by Proetz in 1926. The theory of the treatment is to displace the air in the sinuses and substitute the desired medicament. In the 800 cases in which he has employed such treatment the proportion of improvement with various medicaments was as follows: 25 per cent with foreign proteins, 58 per cent with ephedrine and neosynephrin and 71 per cent with bacterial antigens. Examination and systematic questioning of 100 patients from two to six years after they were discharged revealed that the results were permanent in most cases. Complications have been rare.

## Maine Medical Association Journal, Portland

31:291-314 (Nov.) 1940

- Safeguarding the Surgeon. H. E. Locke, Augusta.—p. 291.  
Pentothal Sodium—Its Field of Usefulness. L. J. Miller and R. M. Tovell, Hartford, Conn.—p. 298.  
Disturbed Physiology of Respiration as Criterion in Choice of Anesthesia. M. Saklad, Providence, R. I.—p. 305.

## Michigan State Medical Society Journal, Muskegon

39:809-904 (Nov.) 1940

- Hypertensive Disease. E. J. Stieglitz, Garrett Park, Md.—p. 827.  
Indirect Blood Transfusion: Vacuum and Pressure Method. W. J. Yott, Detroit.—p. 836.  
Delivery of After-Coming Head: Modification. J. W. Peelen, Kalamazoo.—p. 838.  
Early Carcinoma of Cervix: Diagnosis and Treatment. L. A. Campbell, Saginaw.—p. 839.  
Male Hypogenitalism. W. O. Thompson, Chicago.—p. 842.

## Military Surgeon, Washington, D. C.

87:401-496 (Nov.) 1940

- Organization of the Medical Service of the German Army and Its Employment in the Campaign Against Poland. H. Hartleben.—p. 401.  
Veterinary Inspection of Foods, Its Importance and Responsibility. O. E. McKim.—p. 409.  
Human Convalescent Serum and Vaccination in Prevention and Treatment of Bacillary Dysentery. J. Felsen.—p. 417.  
Use of Cortical Adrenal Extract in Treatment of Severe Burns. H. S. Ivory.—p. 423.  
Value of Intra-Oral Radiographs in Diagnosis, Their Use and Abuse. R. W. Force.—p. 429.  
Accidents in the Army and Their Prevention. S. A. Cohen.—p. 434.  
Observations on Field Medical Service. W. H. Blanchard.—p. 443.  
Facilitate Medical Processing. W. N. Lipscomb.—p. 452.  
Conservation of Health in the Tropics. R. Skelton.—p. 459.  
Surgeon James Mann's Observations on Battlefield Amputations. J. M. Phalen.—p. 463.

## Minnesota Medicine, St. Paul

23:755-824 (Nov.) 1940

- \*Clinical and Surgical Aspects of Spreading Peritonitis Complicating Acute Perforative Appendicitis. J. O. Bower, Philadelphia.—p. 755.  
Diagnosis of Disease of Coronary Arteries. S. M. White, Minneapolis.—p. 767.  
Coronary Disease—Its Treatment. F. J. Hirschboeck, Duluth.—p. 770.  
Electrocardiogram in Coronary Disease. H. Oerting, St. Paul.—p. 775.  
Pneumoconiosis. A. J. Lanza, New York.—p. 776.  
Infected Dermoid Cyst of Thorax Simulating Chronic Empyema. H. K. Gray and R. Woodruff, Rochester.—p. 781.  
\*Observations on Occurrence and Prevention of Sudden Death. J. F. Borg, St. Paul.—p. 783.  
What's Wrong with the Patient Who is Always Tired? W. C. Alvarez, Rochester.—p. 787.  
Polyneuritis with Facial Diplegia (Neuronitis) Following Serum Sickness in Adult. G. R. Kamman and M. Weisberg, St. Paul.—p. 789.  
Primary Adenocarcinoma of Appendix and Carcinoid Tumors. F. C. Schuldt, St. Paul.—p. 791.

**Spreading Peritonitis Complicating Appendicitis.**—Bower points out that the causes for the high mortality of acute appendicitis, as revealed by six surveys, are delay in hospitalization and laxatives. Results of a prophylactic campaign showed a consistent reduction of the mortality in each survey. A prophylactic campaign has been conducted since 1933 throughout the state, and the first statewide survey was completed April 1, 1940. The results indicate that patients do not die from acute appendicitis but from spreading peritonitis, that the prophylactic campaign is the surest method of reducing the mortality and that in considering a plan for prevention of deaths from appendicitis-peritonitis the prophylactic removal of the appendix in the very young must not be overlooked. Deaths can be eradicated by instruction in the schools, as the disease is one of youth. Most deaths occur between the ages of 10 to 20. In Philadelphia high school students have been instructed for ten years, in Pennsylvania for only five. The mortality is 2.44 per cent for Philadelphia and 3.39 per cent for Pennsylvania. Spreading peritonitis causes 92.4 per cent of the appendicitis deaths. The abstracts of 38,085 clinical records show that 1 in 271 died of acute appendicitis, 1 in 49 from appendical abscess and 1 in 4 from spreading peritonitis. Patients admitted to hospitals with acute appendicitis with an intact appendix do not die from the disease, they die a catastrophic death. Of 658 deaths (621 the result of spreading peritonitis) 118 were catastrophes: 29 unavoidable, 89 avoidable. The 29 unavoidable catastrophes represent the hazards coincident to any group of comparable size. Of the avoidable deaths, errors in surgical management were responsible for 71

and errors in diagnosis for 18. Some of the common errors in diagnosis are pneumonia, intestinal obstruction, ruptured cecum, ruptured duodenal ulcer, ruptured gastric ulcer, acute salpingitis, typhoid, diabetes, myelogenous leukemia and otitis media. The common errors in management are appendix ruptured on removal, anesthetic deaths, hemorrhage and post-operative venoclysis. Embolism, cardiac dilatation, coronary disease, myocarditis, thrombosis, atelectasis, apoplexy, pulmonary infarct and uremia caused the 29 unavoidable deaths. Rupture of an acutely inflamed appendix at operation was responsible for the greatest number of the avoidable deaths. This catastrophe occurred once in each 200 patients operated on in the presence of an intact appendix. If a surgeon at operation finds a perforated appendix, if he is doubtful as to whether or not the serous coat is intact or if hemorrhage cannot be controlled by ligature, the insertion of drains is justifiable. In 71 hospitals of the 181 surveyed, 118 operators did not drain the peritoneal cavity following removal of a perforated appendix in 126 patients and 74, or 58.73 per cent, died. What happens when perforations occur early and are accompanied by peritoneal trauma is seen by the following: Twelve of 70 patients operated on lived, 80 per cent of those that died received laxatives. They were operated on forty-eight hours after the onset of symptoms. The average time between perforation and death was 168 hours. These patients were operated on twenty-nine hours earlier and died seventy-two hours sooner than those with localizing processes. Why? Because the vulcanizing plastic-lymph patch was blown off or the cemented intestine or omentum was detached by laxative induced peristalsis. Of 1,118 patients with acute perforations operated on sixty-nine hours after the onset of symptoms 269, or 24.6 per cent, died on an average of two hundred and thirteen hours after the onset of symptoms. Of 1,154 patients admitted with subacute perforations—localizing processes—and operated on ninety-eight hours after the onset of symptoms 281, or 24.35 per cent, died three hundred and fourteen hours after the onset of symptoms. The mortality among 1,080 localized abscesses was 1.2 per cent. Among the 16,046 patients with localized masses the mortality was 0.06 per cent.

**Occurrence and Prevention of Sudden Death.**—Borg believes that sudden death due to ventricular fibrillation might be preventable if it was possible to select patients liable to this condition and counteract the action of epinephrine or to reduce the irritability of the heart muscle. He studied the records of all the patients who among the 22,490 admissions to Ancker Hospital during 1934-1935 died suddenly, unexpectedly and with no indicated or proved structural defect to account for such death. Certain facts emerged from this analysis which indicate the type of patient in which this accident has a tendency to occur. Some contributions indicate that quinidine modifies the action of the substance which presumably produces ventricular fibrillation and thus provides a rational basis for its prevention. During 1936, the third year of the study, quinidine sulfate was administered to patients who seemed liable to sudden death. The study involves 51 patients in whom death was unexpected. It was sudden in appearance and unexplained on a basis of structural change. Postmortem verification was obtained in 25. These deaths were among the 2,570 deaths that occurred in a total of 33,243 admissions to Ancker Hospital, St. Paul, during the three years. Among the 46 unexplained sudden deaths that occurred during 1934 and 1935 there were 39 men and 7 women. These deaths occurred at an advanced age, 76.1 per cent after 60, with the peak decade being that of the seventies. The electrocardiograms of 21 showed abnormal T waves and 8 showed QRS abnormalities, notching, slurring and widening. Twenty-nine had congestive failure, and 17 were in a state of good compensation. Fourteen (30.4 per cent) showed numerous ventricular premature contractions, and auricular fibrillation was present in 7. A definite diagnosis of heart disease was made for all but 2 of the patients. Degenerative heart disease, coronary sclerosis alone or associated with hypertensive heart disease, coronary thrombosis or aortic stenosis accounted for 78.3 per cent of the diagnoses. Sudden death in uncomplicated hypertensive heart disease accounted for only 4 cases, and syphilitic aortitis for 2. In the course of 1936 quinidine sulfate,

3 grains (0.2 Gm.) three times daily, was administered to all patients admitted to the hospital with degenerative heart disease, aortic stenosis or syphilitic aortitis. The drug was given in addition to other indicated therapy and discontinued if not well tolerated. Only 5 sudden deaths occurred, 4 in patients with coronary sclerosis complicated by hypertensive heart disease or coronary thrombosis with congestive heart failure, and 1 in a patient with advanced pulmonary tuberculosis with no recognized cardiovascular disease although permission for necropsy was refused. Of the 4 cases with degenerative heart disease, 3 had not received quinidine. Unless one of these cases is considered as a possible quinidine death, no patient with congestive heart failure who had received the drug in 1936 died suddenly nor did arterial emboli develop. The desirability of the continued use of quinidine to prevent sudden death is open to discussion. No known well controlled studies point to danger, and the present study does not indicate that it exists. The study suggests that a prolonged regimen of quinidine may extend a comfortable and useful existence for many patients with heart disease.

### New England Journal of Medicine, Boston

223:695-744 (Oct. 31) 1940

- The Care of the Patient. C. R. Austrian, Baltimore.—p. 695.  
 \*Diagnosis of Marie-Strümpell Arthritis, with Certain Aspects of Treatment. H. F. Hare, Boston.—p. 702.  
 \*Tuberculous Tenosynovitis. R. Adams, G. Jones and H. C. Marble, Boston.—p. 706.  
 Clinical and Electro-Encephalographic Changes Produced by Sensitive Carotid Sinus of Cerebral Type. J. Romano, E. A. Stead Jr. and Z. Eileen Taylor, Boston.—p. 708.  
 Nontraumatic Dislocation of Atlanto-Axial Joint. S. S. Handig and C. Schlosberg, Cambridge, Mass.—p. 713.  
 Some Epidemiologic Considerations of Diphtheria. V. A. Getting, Boston.—p. 717.

**Marie-Strümpell Arthritis.**—Hare states that during two years 1,179 cases of arthritis were encountered at the Lahey Clinic; 357 of these were of the rheumatoid type, and of these 21 (6 per cent) were of the Marie-Strümpell type. The etiology of the condition is unknown. Presumably it is a form of rheumatoid arthritis usually originating in the sacro-iliac articulations, accompanied or followed by inflammation of the apophyseal joints or vertebral facets. It is a disease of young adults; the symptoms (pain, stiffness and limited spinal motion) start between the ages of 20 and 25 years. It is ten times more frequent in men than in women. The disease may be arbitrarily divided into three phases: the prespondylitic or early stage (characterized by shifting pains of a rheumatic nature in the limbs, chest and peripheral joints), the "sacro-iliitis" phase (during which phase the patient is frequently able to carry on his daily work because the discomfort is more marked at night, several hours after retiring) and as the disease progresses the "pokerback" period (associated with pain along the entire spine, stiffness and eventual rigidity). An increased sedimentation rate is a common observation. Roentgen diagnosis during the prespondylitic stage is not possible, as there are no demonstrable osseous or ligamentous changes. During the phase of sacro-iliitis definite osseous changes may involve the sacro-iliac articulations, consisting of symmetrical changes of the sacro-iliac region, with increased density or osteosclerotic reaction surrounding the joint, with slight narrowing of the joint spaces. As the disease progresses, changes gradually become apparent around the apophyseal joints or articulating facets, the joint spaces appearing narrowed or obliterated. Decalcification of the vertebrae and still later calcification of the ligaments may be observed. Gradually the entire spine appears to be fitted with a calcified casing partially obliterating the individual bony structures. This is known as the "bamboo" spine. The condition may be confused most frequently with degenerative arthritis, metastatic cancer, Paget's disease and other types of rheumatoid arthritis. Bed rest with the spine held in extension has been successful in relieving pain and preventing and correcting deformities, but because the disease is slowly progressive it must be carried out over a long time during which there is gradual muscle wasting, and rehabilitation becomes necessary. Swaim suggests putting the patient to bed until pain is relieved and then giving him a form-fitting jacket to wear. This has been successful in preventing deformities and, according to him, largely relieves pain and prevents involvement of the peripheral joints.

Hare has found that roentgen therapy relieves pain in about 80 per cent of cases. The maximal number of treatments given to any one patient has been twenty. A patient, followed for two years, has received no treatment during the last year and has had no discomfort. The best test of radiation therapy has been that 33 of the 35 patients seen at the clinic during three years are now able to work; this includes 5 patients who were formerly incapacitated. Radiation therapy is directed to the entire spine, the sacro-iliac joints and the paravertebral and gluteal muscles. Small doses give relief. The author uses six portals of 300 sq. cm. each and treats one portal daily, administering 300 roentgens to each portal. The following factors are employed: from 150 to 200 kilovolts, 20 milliamperes, from 0.25 to 0.5 mm. of copper and 1 mm. of aluminum filters and a distance of 50 cm. Relief of pain may occur during the first week, or two or three weeks following irradiation. If pain recurs it may usually be relieved by a single small dose of roentgen rays. When pain is relieved it is advisable to refer the patient to the orthopedic surgeon for muscle-building exercises and correction of existing deformities.

**Tuberculous Tenosynovitis.**—Adams and his co-workers analyze the diagnostic and therapeutic features of the 36 cases of tuberculous tenosynovitis observed at the Massachusetts General Hospital during the last forty-five years. The youngest patient, complaining of symptoms for a year and a half, was 15 years of age; the oldest patient was 75 and had had symptoms for three years when first seen. The average age of the patients was 36 years. There were 21 males and 15 females. The right hand was involved twenty-two times and the left hand fourteen times. The volar surface was involved twenty-five and the dorsal surface thirteen times. The influence of use on incidence is shown by the high involvement of the right hand. The occupations varied widely. There were no laborers, but 30 patients made hard use of their hands. Eight patients complained of definite antecedent trauma. Thirteen of the patients had tuberculosis elsewhere in the body. Diagnosis in the early stages may be difficult. The typical feature is a gradually developing, painless or slightly tender mass on the volar aspect of the hand. Partial stiffness with inability completely to flex or to extend the fingers and diminished strength on grasping are common. One of the most valuable diagnostic aids is a four hour temperature chart over a period of several days. A daily rise in temperature to 99.6 or 100.6 F. is suggestive of tuberculosis and should lead to further study. In suspected cases, splinting should be employed from the beginning. Finger motion in the later stages of the disease may cause creaking or grating sounds because of degenerated fibrinous deposits within the tendon sheath—so-called rice bodies. Joint stiffness and a fluctuant mass often indicate osseous disease, which may be proved by roentgen demonstration of destruction of the carpus. The diagnosis was proved pathologically in 27 of the cases and established beyond a reasonable clinical doubt in 9. The diagnosis of tuberculous tenosynovitis has been equivalent to the recommendation of operation; 33 of the 36 patients were so treated. Incision and drainage of fluctuant masses was carried out in 9 cases and resection of the involved tendon sheaths in 24. Follow-up notes are available in 26 of the 36 cases and in 23 of the ones in which operation was performed. Two of the 3 patients not operated on recovered completely and resumed their work. The third is unimproved and suffers also from pulmonary tuberculosis. Of the 23 patients who were operated on 7 are unimproved, 8 are improved and 8 have the condition in an arrested form. The best results were obtained when operation was performed during the second or third year of the disease. These results are none too good. No other tuberculous condition, with the possible exception of tuberculous lymph nodes of the neck, has been subjected to surgery with such casualness and lack of accessory data. Tuberculosis of the tendon sheaths should receive the same systemic treatment accorded to tuberculosis of the lungs or spine. Surgical attack on a tuberculous focus such as a tendon sheath without knowledge of how the lesion is progressing involves the likelihood of operating in the presence of advancing or exudative disease. Such knowledge can be gained only by periodic observation, during which time treatment in the form of splint immobilization and sanatorium type of care should be given. The tuberculous patient must demonstrate resistance and

an ability to localize infection before operation is considered. Attempts at extirpation under other circumstances constitute meddlesome surgery. Drainage procedures for abscesses about the hand to relieve mechanical pressure often bring relief of symptoms but rarely arrest the disease, because the active focus remains. Kanavel has stated that complete removal of tuberculous tendon sheaths or tuberculous tendons will effect a cure. If true, this means that before excision the exudative phase must be over and the fibrotic phase well under way. Six of the authors' 10 arrested cases were instances in which the hand was disabled by the sequelae of an infection that became quiescent; that is, by fibrosis of tendon sheaths, adherent tendons and rice bodies.

223:745-788 (Nov. 7) 1940

- Insulin Resistance: Report of Case. J. F. Regan, J. J. Westra and R. M. Wilder, Rochester, Minn.—p. 745.  
\*Treatment of Leukemia by Radioactive Phosphorus. S. Warren, Boston.—p. 751.  
Notes on History of Rheumatism and Gout. R. S. Hormell, Boston.—p. 754.  
\*Carcinoma of Breast in 10 Year Old Girl: Report of Case. J. B. Sears and M. J. Schlesinger, Boston.—p. 760.  
Treatment of Lobar Pneumonia with Sulfathiazole and Sulfapyridine. M. Cutts, A. M. Burgess and F. H. Chafee, Providence, R. I.—p. 762.  
Cardiology: I. Management of Cardiac Patients Who Require Major Surgery: II. Treatment of Cardiac Arrhythmias. H. L. Blumgart, Boston.—p. 765.

**Treatment of Leukemia by Radioactive Phosphorus.**—Warren calls attention to experiments on the effect of radiation from temporarily radioactive phosphorus on cells and tissues and to cases of leukemia which were treated by Lawrence and his associates with radioactive phosphorus from the Berkeley cyclotron. The author selected for this treatment cases of acute and subacute leukemia, since in them the established methods of radiation therapy leave much to be desired. The radioactive phosphorus was chiefly obtained from the Harvard cyclotron. Red phosphorus bombarded in the target chamber of the cyclotron was utilized in the beginning. Later, in order to obtain a more concentrated source, phosphorus in the form of iron phosphide was placed on a probe within the deuterium stream of the cyclotron. A portion of the phosphorus was thus made radioactive. This phosphorus has a half-life of 14.5 days and gives off a fairly penetrating beta radiation. The phosphorus thus treated was changed by standard chemical methods to dibasic sodium phosphate. This was calibrated as to radioactivity on a modified Lauritsen type electroscope. The desired amount of radioactive phosphorus, ranging from 1 to 4 millicurie equivalents, was dissolved in 5 per cent dextrose and physiologic solution of sodium chloride prepared for intravenous use, sterilized and injected intravenously into the patients. Animal experiments show that the injected phosphorus is absorbed selectively in the various organs and tissues. Fortunately, those in which the major deposit of leukemic cells occurs (bones, liver, kidneys and spleen) take up relatively large amounts. In all cases the excretion of radioactive phosphorus was followed in the urine. The concentration in the blood was checked from time to time in order that excessive doses might not be given. Large doses of radioactive phosphorus have been shown to produce marked fibrosis and aplasia of the hemopoietic tissues. The author presents 4 case reports in which this treatment was employed. Some improvement was seen in 2 patients as evidenced by their general condition, level of white cell count and the state of the bone marrow. These patients are moderately active. Two patients showed no significant response beyond minor changes in white cell count; both have since died. This therapy is experimental and does not displace present methods of irradiation in the treatment of leukemia.

**Carcinoma of Breast in 10 Year Old Girl.**—According to Sears and Schlesinger, only 2 well authenticated cases of breast cancer before puberty have been reported in the last three decades. They concerned girls of 11 and 12 years, respectively. The authors present the history of a girl, aged 10, who was brought to their hospital because of a lump in the right breast. Six years previously her mother had noted the lump. The child said she had hit her right chest on a car door that day. The mother believed that it might have grown during the previous year. There was no history of pain or tenderness. Physical examination revealed a nodule

3 by 2.5 by 2.5 cm. under the right nipple. It was hard, irregular, sharply circumscribed, nontender and adherent to the overlying nipple, which was flattened. Roentgen examination of the tumor showed no evidence of calcification; that of the long bones, skull and chest showed no evidence of metastases. The breast tumor and pectoral fascia were excised. A curved incision was made along the lower aspect of the tumor, which was exposed and found to be resting on the pectoral fascia. Immediate examination by frozen section disclosed a carcinoma. A wide area of skin was excised, together with the fascia overlying the pectoralis major. No lymph nodes were felt on the border of the pectoralis or in the axilla. The wound was closed without drainage. At the end of the year there was no evidence of recurrence.

### New Jersey Medical Society Journal, Trenton

37:529-566 (Nov.) 1940

- Diarrhea: Causes and Treatment. M. Kraemer, Newark.—p. 533.  
Differential Diagnosis of Neoplasm and Primary Vascular Disease of Intracranial Cavity. J. Browder, Brooklyn.—p. 537.  
Movements of Human Uterus Before and During Labor. D. P. Murphy, Philadelphia.—p. 538.

### New Orleans Medical and Surgical Journal

93:223-276 (Nov.) 1940

- Carcinoma of Pancreas: Clinical Review of Eight Cases. T. P. Lloyd and W. F. Drummond, Shreveport, La.—p. 223.  
Cause and Prevention of Loss of Teeth. C. C. Bass, New Orleans.—p. 227.  
Advanced Pathology of Esophagus: Report of Case. J. E. Knighton Jr., Shreveport, La.—p. 231.  
Immunization Against Disease in Infants and Children. H. A. White, Alexandria, La.—p. 236.  
Rheumatic Infection in Children in the Deep South. J. E. Bailey, New Orleans.—p. 240.  
Some Facts About Premature Infants. C. T. Williams, New Orleans.—p. 244.  
Indications and Contraindications for Surgical Intervention in Treatment of Abortion. P. Graffagnino, New Orleans.—p. 247.  
Why We Should Be Familiar with Roentgenologic Appearance of Developmental Changes of Skeleton. A. Mayoral, New Orleans.—p. 250.  
Glaucoma: Responsibility of the General Practitioner. M. C. Wilensky, New Orleans.—p. 254.  
Splenectomy and Purpura Haemorrhagica. M. Finn, New Orleans.—p. 259.

### New York State Journal of Medicine, New York

40:1557-1624 (Nov. 1) 1940

- Cryotherapy and Its Relation to Hibernation. W. L. Whittemore, J. R. Lisa and P. K. Sauer, New York.—p. 1563.  
Treatment of Some Common Disfigurements of the Skin. A. B. Cannon, New York.—p. 1567.  
Problems in Diagnosis and Treatment of Recurring Vesicular Eruptions of Hands. F. Wise and J. Wolf, New York.—p. 1573.  
Fluorography: Its Technic and Application. I. S. Hirsch, New York.—p. 1579.  
Physical Defects and Juvenile Delinquency. E. W. Wallace, Buffalo.—p. 1586.  
Responsibility of the Pediatrician in Regard to Children's Eyes. B. F. Payne, New York.—p. 1591.  
Infrequency of Toxoid Reactions in 11,326 School Children. J. H. Landes, New York.—p. 1594.  
Report of Intensive Laboratory Studies of High School Athletes. L. S. Preston, Oneida.—p. 1599.  
The School Physician and the Care of the Athlete. R. H. Broad, Ithaca.—p. 1603.  
Vertebral Hemangioma with Neurologic Symptoms. L. M. C. Kelly, New York.—p. 1607.

40:1625-1692 (Nov. 15) 1940

- Progress in Ophthalmology. A. J. Bedell, Albany.—p. 1631.  
Chronic Heart Diseases—Diagnosis and Treatment. C. E. de la Chapelle, New York.—p. 1638.  
Causes and Relief of Symptoms Following Cholecystectomy. R. F. Carter and B. Marraffino, New York.—p. 1648.  
Chronic Nontuberculous Renal Infections: Their Significance and Treatment. W. W. Scott, Rochester.—p. 1655.

### Northwest Medicine, Seattle

39:393-434 (Nov.) 1940

- Ileostomy Preliminary to Resection of Gastrojejunal Colic Fistula. J. W. Baker, Seattle.—p. 398.  
Diagnostic Considerations of Intracranial Neoplasms. A. L. Saks, Iowa City.—p. 403.  
Diagnosis of Brain Tumor. P. G. Flothow, Seattle.—p. 406.  
Headaches. E. D. Warren, Tacoma, Wash.—p. 412.  
Vascular Syndrome Headache: Report of Case with Note on Mechanism of Histamine Therapy. J. H. Besson, Portland, Ore.—p. 416.  
Treatment with Vitamins. D. L. Wilbur, San Francisco.—p. 417.

## Surgery, St. Louis

8:739-902 (Nov.) 1940

- \*Congenital Prepyloric Membranous Obstruction in Premature Infant. A. S. W. Touroff and R. M. Sussman, New York.—p. 739.
- Cerebral Herniation Through Incisura Tentorii: Clinical, Pathologic and Experimental Study. W. L. Reid, Montreal.—p. 756.
- \*Cerebellar Subdural Hematoma in Infant 2 Weeks Old with Secondary Hydrocephalus: Operation with Recovery. R. G. Coblentz, Baltimore.—p. 771.
- Note on Straightening the Hypospadiac Penis. C. D. Creevy, Minneapolis.—p. 777.
- Hypospadias. H. W. Meyer, New York.—p. 781.
- Improved Apparatus for Tidal Drainage of Urinary Bladder and Empyema Cavities. C. J. Bellis, Minneapolis.—p. 791.
- Perineal Prostatectomy: Modification of Closure. S. A. Vest, University, Va.—p. 798.
- Principles and Practice of Radical Operations for Hernia. E. Pölya, Budapest, Hungary.—p. 804.
- Osteomyelitis of Jaws: Analysis of Fifty-Nine Patients. E. C. Padgett, Kansas City, Mo.—p. 821.
- \*Paravertebral Procaine Block in Treatment of Postoperative Atelectasis: Preliminary Report. J. A. Gius, Portland, Ore.—p. 832.
- Study of Capillary Permeability and Inflammation in Skin of Rabbit Given Adrenalin. R. H. Rigdon, Memphis, Tenn.—p. 839.

**Congenital Prepyloric Obstruction.**—Touroff and Sussman report a case of congenital gastric obstruction in a premature infant due to a complete prepyloric septum of mucous membrane. Three and possibly all 4 offspring of the patient's father and the father's 2 sisters suffered from some congenital anomaly; all but the patient died in infancy. Symptoms of high obstruction commenced at birth. Additional features were failure of the child to pass meconium, and icterus which was more intense than normal. These manifestations suggested additional obstructive anomalies of the lower intestinal tract and biliary duct system. Roentgen examination revealed an obstructive lesion in the distal portion of the stomach or first portion of the duodenum. Operation, on the fifth day of life, consisted of multiple incisions of the prepyloric septum and pyloroplasty. No other anomalies were found. The early postoperative course was uneventful. The icterus was concluded to be an accompaniment of prematurity and failure to pass meconium as due to a lack of the normal stimulus to intestinal peristalsis, which apparently is initiated by the passage of gastric contents into the duodenum. On the eighteenth postoperative day a secondary, complete intestinal obstruction developed, and five days later, when another operation was about to be performed, the obstruction was relieved spontaneously. The course thereafter, although temporarily stormy, was one of improvement ending in recovery. Roentgenograms taken five months after operation revealed the gastrointestinal tract to be normal except for rapid emptying of the stomach and intestinal hypermotility. The follow-up period now is seventeen months. To the authors' knowledge the case is the first of its kind to be reported.

**Cerebellar Subdural Hematoma.**—Coblentz presents the history of an infant of 2 weeks who recovered after an operation for an encysted subdural hematoma. The author believes that his is the first case to be recognized during life and cured by operation. The hematoma was located over the right cerebellar hemisphere. Secondary hydrocephalus also was present. Although there was no definite history of trauma, ecchymosis of the upper lids and a moderate occipital caput led the author to suspect slight trauma as the most likely etiologic factor. Prompt disappearance of blood in the lumbar subarachnoid fluid after daily lumbar punctures and continued increased intracranial pressure indicated a coexisting lesion. Subdural hematoma over the cerebellar hemispheres was ruled out by subdural taps. Ventriculography definitely located the lesion in the posterior fossa. Evacuation of the clot through a small trephine opening without drainage effected a cure. At the time of writing, the baby is 3 months old and has made a complete recovery.

**Paravertebral Procaine Block for Postoperative Atelectasis.**—Gius treated successfully 2 cases of postoperative atelectasis in children by paravertebral block anesthesia of the operative wound. He suggests that this procedure, which temporarily abolishes pain in the wound and allows for active hyper-ventilation of the lungs and effective coughing, may prove to be an important adjunct to the methods now used for combating the condition. The operative wound must be supported so that the possibility of separation following violent coughing will be obviated. During the period when atelectasis is most likely to occur, catgut sutures are said to retain their maximal strength.

The added strain of severe coughing may occasionally break or tear out the sutures, but urgent measures are warranted if atelectasis is to be avoided. The author points out that the results in his 2 cases were so striking that there seems to be no doubt that anesthesia of the wound was a significant factor in the rapid clearance of symptoms and signs. These cases can hardly be regarded as a conclusive test of the procedure, yet the results observed convince him that the method is practical.

## Texas State Journal of Medicine, Fort Worth

36:463-526 (Nov.) 1940

- Extrinsic Lesions of Heart. C. S. Beck, Cleveland.—p. 468.
- Evolution of Major Surgery in Treatment of Pulmonary Tuberculosis. L. F. Knoepf, Shreveport, La.—p. 472.
- Systematic Use of Strophanthin in Treatment of Decompensation of Heart. F. V. Grunbaum, Houston.—p. 476.
- Abdominal Conditions in Children, with Special Reference to the Mechanical Appendix. A. Brown, Toronto.—p. 482.
- Acute Leukemias. W. N. Powell, Temple.—p. 486.
- Diagnosis and Treatment of Cancer of Pharynx. A. C. Christie, Washington, D. C.—p. 490.
- Prenatal Blood Changes. R. L. Grogan, Fort Worth.—p. 494.
- Management of Certain Perforating Wounds of Eyeball: Report of Cases. E. M. Sykes, San Antonio.—p. 497.
- The Training of Medical Technologists in Texas. J. J. Andujar, Fort Worth.—p. 503.
- Spasm of Inferior Oblique with Head Tilt. M. K. McCullough, Dallas.—p. 507.

## Western J. Surg., Obst. &amp; Gynecology, Portland, Ore.

48:645-714 (Nov.) 1940

- Consideration of Recent Additions to Clinical and Experimental Knowledge of Breast Conditions. F. E. Adair, New York.—p. 645.
- Value of Oxygen and of Helium-Oxygen Mixtures Before and After Thyroidectomy. W. M. Boothby and S. F. Haines, Rochester, Minn.—p. 662.
- Treatment of Traumatic Brain Injuries. P. G. Flothow, Seattle.—p. 670.
- \*Incidence of Venereal Diseases in Cases of Male Impotence and Male Sterility. M. Huhner, New York.—p. 676.
- Clinical versus "Pathologic" Appendicitis. C. A. Bachhuber and W. A. Bayley, Los Angeles.—p. 677.
- New Method of Colostomy and Ileostomy. M. E. Steinberg, Portland, Ore.—p. 682.
- Final Report of Case of Malignant Adenoma of Parathyroid Glands. E. M. Hall and L. Chaffin, Los Angeles.—p. 685.
- Value of Electroencephalogram in Craniocerebral Injuries. M. A. Glaser and H. Sjaardema, Los Angeles.—p. 689.
- Congenital Equinovarus. L. Cozen, Los Angeles, and W. Greene, Boston.—p. 697.
- Diagnosis and Curability of Papillary Adenocarcinoma of Thyroid Gland: Case Report. F. S. Wetherell, Syracuse, N. Y.—p. 707.

## Venereal Disease, Male Impotence and Sterility.—

Huhner, in studying the records of 800 consecutive cases of male impotence, found that 30 per cent of them had a history of previous venereal infection; likewise a similar history was given by 36 per cent of more than 200 sterile men. These figures contrast well with the statistics of gonorrhea, which show that about 80 per cent of unmarried men less than 30 years of age have had at least one gonorrheal infection. The great majority of the venereal infections among the author's patients were gonorrheal. A history of syphilis was a rarity in either the impotence or the sterility cases. However, in the majority of cases the gonorrhea had been acquired when the patient was quite young and had been cured permanently many years before the onset of the impotence. Gonorrhea is really hardly ever a cause of male impotence. Azoospermia is found in a large number of cases of male sterility. The condition is due to occlusion of the vasa due to an untreated or badly treated gonorrhea in which the infection passed into the posterior urethra and into the vasa. As a rule the gonorrheal infection stops with the occlusion of the tubes, but occasionally it goes still further and in some manner destroys the spermatogenic function of the testicles.

## West Virginia Medical Journal, Charleston

36:489-536 (Nov.) 1940

- Treatment of Sinusitis. W. C. Bowers, New York.—p. 489.
- Appendicitis: Analysis of 1,588 Cases Treated Surgically. H. G. Camper and H. A. Bracey, Welch.—p. 499.
- Management of Acute Appendicitis—Arguments and Controversies. H. B. Stone, Baltimore.—p. 505.
- Conception of Cancer as Related to Preoperative Irradiation. R. M. Caulk, Washington, D. C.—p. 511.
- Traumatic Appendicitis: Report of Case. C. H. Engelfried, Montgomery.—p. 516.



## FOREIGN

An asterisk (\*) before a title indicates that the article is abstracted below. Single case reports and trials of new drugs are usually omitted.

## British Medical Journal, London

2:513-544 (Oct. 19) 1940

- Role of Liver in Diabetes Mellitus. G. Graham.—p. 513.  
Sulphydryl Compounds and Wound Repair. J. F. Riley.—p. 516.  
Respirator as an Oxygen Apparatus. H. L. Marriott.—p. 519.  
\*Contusion of Myocardium. H. Barber.—p. 520.  
Anaphylaxis After Injection of Tetanus Toxoid. A. A. Cunningham.—p. 522.

**Contusion of Myocardium.**—Barber points out that a blow over the chest or compression of the thorax may cause a variety of traumatic heart lesions. The site of the cardiac lesion is not necessarily related to the site of the blow. The anterior aspect of the right ventricle is injured most frequently. There are many records of myocardial injury in the absence of fractures or signs of external bruising. During the last two years in studying heart injuries in fatal accidents the author found that they are more frequent than expected. He gave particular attention to less serious lesions, compatible with recovery of patients who died from causes apart from the heart. These have been sufficient in number to suggest that recovery from undiagnosed myocardial contusion is by no means rare. The most convincing evidence that a blow over the chest may injure the myocardium is obtained from records of cases described as delayed rupture of the heart. An example is that of a young man who was struck over the front of the chest by a cricket ball. After a short interval he continued to play throughout that and the second day. The second evening he complained of pain in the chest and died shortly afterward. At necropsy a rupture of the right ventricle was seen, with hemorrhage into the pericardium. Rupture occurred at varying intervals, most commonly between one and two weeks after the injury, but sometimes considerably later. This rare event is probably the result of a blow which ruptures the endocardium. Physical signs of localized myocardial injury are negligible unless some transient changes in the T wave of the electrocardiogram can be detected. In trauma to a valve the symptoms of distress are immediate, but in myocardial contusion there may be an interval between the injury and the more obvious symptoms. If there has been a chest injury, whether severe or apparently slight, any symptom suggesting heart disability must be considered. There may be dyspnea, a feeling of oppression in the chest, perhaps with anginal pain, and possibly the expectoration of frothy sputum. Obvious symptoms followed by complete recovery furnish reasonably clear proof of a contusion. Routine roentgen examination of chest injuries in the accident wards might reveal unsuspected hemorrhagic pericardial effusions. The symptoms which follow a blow may arise when the contusion involves the pericardium. A permanently inefficient heart, myocardial weakness, may follow trauma such as fracture of several ribs. Such patients differ from those with effort syndrome in that they usually are quite free from the nervous element. Barber and Osborn have reported the finding at necropsy of a deep-seated scar in the heart muscle twenty-two years after trauma to the mitral valve. Heart block, especially temporary, following trauma may be considered as proof of a deep-seated contusion. Clinical signs typical of angina pectoris, auricular fibrillation or valve rupture may follow a blow over the chest. The clinical history and the clinical features are the most important diagnostic guides.

## Medical Journal of Australia, Sydney

2:301-330 (Oct. 5) 1940

- \*Management of Cerebral Gliomas. G. Phillips.—p. 301.  
\*Use of Histamine in Treatment of Neurovascular Headache. W. L. Reid.—p. 307.

**Cerebral Gliomas.**—Phillips reports two deaths in a series of 35 consecutive cases of cerebral or cerebellar tumors removed surgically. One death occurred eight weeks after operation as a result of an accident, while the other occurred fourteen days after operation as the result of intracranial hemorrhage. Twenty-eight of the 35 operations were performed in the presence of a large space-occupying lesion in the skull associated in each instance

with a considerable increase of intracranial pressure; 1 patient died as the result of late wound infection. The results substantiate the claim that with adequate management cerebral tumors may be exposed and removed with a relatively low surgical mortality rate. Operation under local anesthesia makes this possible. The patient's ability to complain of pain, cold and discomfort, and the opportunity to provide adequate fluid by mouth during prolonged surgical procedures, are constant guardians against cerebral shock. Except in children, the author rarely uses general anesthesia. Twenty-two of the intracranial tumors were gliomas. In 10 cases the whole tumor was removed, the greater part of the tumor in another 8, and in 4 for various reasons no attempt was made to remove the tumor, which after exposure was treated by high voltage roentgen radiation. The author believes that, irrespective of the skill of the surgeon, operations for cerebral glioma will frequently be succeeded by a fatality if these tumors are lumped together as a single group and submitted to indiscriminate surgery. Particularly is this so since nearly 40 per cent are glioblastomas. A major responsibility for the surgeon is to equip himself with the frequency, location statistics and full life history of cerebral gliomas. The capacity for diagnosing cerebral gliomas preoperatively is almost the sine qua non of continued success. The pertinent facts regarding glioma are as follows: The percentages for the different types of gliomas are: glioblastomas 40, astrocytomas 40, medulloblastomas 12, oligodendrogliomas 2, ependymomas 2 and all the rare types 4. The average postoperative survival period for the respective tumors has been twelve months, from six to ten years, from two to four years, more than six years and for the rare types the survival time is variable. The average age at which glioblastomas occur is between 40 and 60, for astrocytomas of the cerebrum it is 30 and for those of the cerebellum 13, for the medulloblastomas 10 and oligodendrogliomas 30 years; the ependymomas and the rare types occur at various ages.

**Histamine for Neurovascular Headache.**—Reid gave small repeated subcutaneous doses of histamine to 5 patients with neurovascular type of headache. One patient experienced only partial relief, while the other 4 obtained complete relief. Each patient, after the possibility of an intracranial pathologic lesion was excluded and the patient reacted positively to an intradermal test injection of histamine, was given graduated doses of histamine in the following manner: The solution used consisted of 1 mg. of histamine dissolved in 10 cc. of physiologic solution of sodium chloride. On the first and second days 0.05 mg. of histamine (0.5 cc. of the solution) was injected subcutaneously twice a day; on the third and fourth days, 0.075 mg. (0.75 cc. of the solution). Thereafter, up to the end of the third week, 0.1 mg. (1 cc. of the solution) was given twice a day. When this course was finished, each patient was given one injection of 0.1 mg. of histamine once a week. If the patient remained free from symptoms during the next two or three months, an attempt was made to decrease the dose by spacing the injections. If the symptoms recurred after the dose was diminished, the injections were again increased to one a week. The author applies the term "neurovascular headache" because there is fairly conclusive proof that the aura and pain in many complaints of head pain are due to a disturbance of the neurovascular mechanism controlling certain intracranial and extracranial blood vessels. Of the various patterns of this group, migraine is perhaps the best known. There are several other patterns which have a neurovascular mechanism, and some of these are as common as the classic migraine. It is emphasized that the use of histamine must not be regarded as a cure-all for every type of headache. Each case must be thoroughly investigated and only when all possibility of a pathologic lesion has been excluded should a neurovascular mechanism be considered.

## South African Medical Journal, Cape Town

14:351-370 (Sept. 28) 1940

- Sterility in Women and Its Treatment. G. S. van der Merwe.—p. 355.  
Dermatitis Artefacta. J. A. Levitt, S. Gordon and M. J. Cohen.—p. 359.  
Observations on Fractures of Shaft of Femur. S. V. Humphries.—p. 362.



**Schweizerische medizinische Wochenschrift, Basel**

70:901-924 (Sept. 21) 1940. Partial Index

Fluid Current in Blood, Tissue Clefts and Lymph Channels. O. Müller. p. 901.

Experiences with Erection of Vertebral Fractures. A. Fehr.—p. 906.

Cytotoxicology of Some Pharmaceutical Preparations (Arsenic, Colchicine, Acridiflavine Hydrochloride, Nicotine and Nikethamide) on Basis of Investigations on Tissue Cultures. O. Bucher.—p. 910.

\*Problems of Physiologically Correct Bread-Grain Food. W. Kraft.—p. 913.

**Physiologically Correct Bread.**—According to Kraft, increased knowledge regarding vitamins and mineral substances has terminated the dispute about the degree of utilization of bread grains and has established the principle of complete utilization of the grain. He describes the structure of the cereal grain and the production of flour. Eight decades ago the production of flour was changed in such a manner that the most valuable parts of the grain, the cereal germ and the external layers, were removed during the process of milling. Since these parts contain valuable proteins, vitamins, lipoids, ferments, minerals, cellulose and pectins, the resulting flour was much inferior to the whole grain flour of the older days. The author stresses particularly the loss of vitamin B<sub>1</sub> from the "fine" flour produced by modern methods of milling. He discusses the vitamin B<sub>1</sub> requirements of the human organism and stresses the necessity of returning to the use of whole grain flour. The bread which has been introduced during the war, although it utilizes the grain to a fuller extent than was the case before, is still inadequate because the germ and part of the external layers are still being eliminated for the reason that flours which retain these parts are not suitable for long storage. The author suggests that the entire grain be utilized and that only fresh flour be used for the production of bread. It is better to bake the flat type of bread than the loaf type when using flour from whole grain.

**Riforma Medica, Naples**

56:971-996 (Aug. 3) 1940. Partial Index

\*Vertebral Pseudarthrosis. V. Putti.—p. 971.

Internal Leishmaniasis and Reticulo-Endothelial System. G. Murano.—p. 975.

**Vertebral Pseudarthrosis.**—Putti reports roentgenologic studies of the spine in several cases of so-called Kümmell's disease. He believes that the condition is a pseudarthrosis resulting from a vertebral fracture that has not been immobilized. Failure to place the fragments in a position favorable for consolidation results in lack of formation of callus, absorption of the surfaces of the bony fragments that are in contact and erosion of one of the surfaces from improper contact with the opposing surface. The treatment is that of pseudarthrosis and consists of prolonged immobilization for reduction and consolidation of small fractures of short duration, and of prolonged immobilization after transplantation of small bone fragments in cases of long duration, especially if the fracture is complicated by porosis of the vertebra. The author reports 3 cases. In 1 the fracture occurred twenty-two years ago. Functional, painful symptoms became aggravated whenever the patient attempted to follow a moderately active existence. A gibbus developed sixteen years after occurrence of the fracture. Satisfactory anatomic and functional results were obtained from vertebral osteosynthesis with two tibial fragments followed by prolonged immobilization in a cast. The author emphasizes the importance of roentgen examination of the spine in all cases of vertebral trauma for the early diagnosis and treatment of vertebral fractures and prevention of vertebral pseudarthrosis.

**Archiv für Kinderheilkunde, Stuttgart**

120:1-48 (May 31) 1940

Observation on a Virus in German Measles. H. Steinmaurer.—p. 1.

\*Treatment of Toxic Diphtheria with Large Doses of Serum and Ascorbic Acid. F. Szirmai.—p. 23.

Anemia of the Newborn. Maria Mainka.—p. 40.

**Serum and Ascorbic Acid in Toxic Diphtheria.**—

According to Szirmai, many investigators have demonstrated that ascorbic acid neutralizes the toxin of diphtheria not only in the test tube but also in the living organism and that it increases the resistance of experimental animals against this toxin. In addition to clinical experience the author made experimental studies by testing the effect of ascorbic acid on

the Schick reaction. Observations made in the course of these experiments indicate that in the treatment of diphtheria only ascorbic acid itself and not its neutralized solutions should be used. The author thinks that the action of ascorbic acid is due to its nonspecific detoxication of the diphtheria toxin. It has not been definitely decided whether the oral or the intravenous administration of ascorbic acid is the best, and whether saturation of the organism is necessary. According to Friedemann's classification there are two types of toxic diphtheria which differ in regard to their prognosis, the edematous and the hemorrhagic-necrotic type. The more frequent and less malignant edematous type is characterized by edema (often unilateral) of the soft palate, gelatinous, infiltrated and slightly formed pseudomembranes and by indistinctly outlined cervical lymph nodes surrounded by subcutaneous edema. In the hemorrhagic necrotic type the membranes are likewise not extensive at first, but they are circular or oval, sharply defined and thick and of a dirty brownish red and later spread rapidly. A bloody, irritating nasal discharge and cutaneous and mucous hemorrhages appear. In both forms there exist foetor ex ore and adenoiditis with impaired nasal breathing. If serotherapy is begun too late or is inadequate, albuminuria, restlessness, pallor and myocarditic symptoms develop. The local and generalized symptoms in which malignant diphtheria differs from simple pharyngeal diphtheria are regarded by the author as the manifestation of an intensive action of diphtheria toxin, but the formation of the pseudomembrane he regards as a direct action of the diphtheria bacilli. He considers the edema and the hemorrhagic necroses and not the pseudomembranes as the characteristics of malignant toxic diphtheria. In the edematous form of toxic diphtheria, he was able to reduce the mortality greatly by the simultaneous administration of large doses of serum, intravenously as well as intramuscularly, and of ascorbic acid. Whereas before the introduction of this combination therapy fifteen fatalities occurred among 54 edematous cases of malignant diphtheria (27.8 per cent), only one occurred in 18 cases (5.5 per cent) with this combination therapy. The success of this treatment depends on the recognition of early signs of toxicity. The author is unable to say whether the combined administration of large doses of serum and ascorbic acid will be effective also in the hemorrhagic-necrotic form of toxic diphtheria, for no cases of this type were observed in the last few years.

**Deutsche medizinische Wochenschrift, Leipzig**

66:309-336 (March 22) 1940. Partial Index

Early Symptoms of Tumors of Spinal Cord. M. de Crinis.—p. 309.

Diagnosis of Comotio Cerebri. E. Bay.—p. 312.

\*Importance of Skull Trauma for Development of Organic Cerebral Changes. H.-H. Meyer.—p. 316.

\*Full Extracts of Belladonna in Therapy of Encephalitis. F. Scheiffarth.—p. 318.

Tumor of Spinal Cord and Diabetes. L. Roemheld.—p. 321.

Reduction of Intra-Ocular Pressure in Poisoning with Salicylic Acid Preparations. J. Váradý and F. Jahn.—p. 322.

Demonstration of Erythrocytes with Basophil Stippling in Sternal Puncture of Patients with Lead Poisoning. N. Henning and H. Keilback.—p. 323.

**Skull Trauma and Organic Cerebral Changes.**—According to Meyer, the importance of skull trauma for the brain has received greater attention in recent years because of the increase in traffic accidents. He reports two cases, in both of which the skull trauma seemed to be of a harmless nature. There had been no injury to the bones of the skull nor had there been loss of consciousness or vomiting. Acute exacerbation developed after four and thirty-one days respectively, probably as the result of a hemorrhage. One patient developed hemiplegia and speech disturbance, and the other symptoms of pressure on the brain and epileptiform attacks. These cases demonstrate that the lack of symptoms immediately after the trauma does not prove that the brain has escaped injury. The interval between the trauma and the appearance of severe cerebral symptoms may vary greatly. There have been cases of skull trauma in which epileptiform attacks, jacksonian attacks and metabolic disturbances developed years later. Encephalographic examination is an important aid in many cases. The displacement and widening of the ventricles and differences in the visualized subarachnoid space permit important conclusions. It may be assumed that such changes are partly due to tissue

destruction, to shrinkage of the tissues or to glial scars and tensions produced by cicatrices. Great care is necessary in the estimation of encephalographic pictures, because not all changes have a traumatic origin. If these are observed in cases in which the history reveals a cranial trauma, one is justified in ascribing them to this trauma.

**Belladonna in Therapy of Encephalitis.**—Scheiffarth reviews observations made in the course of treatment of encephalitic and other extrapyramidal disturbances. In his discussion of the pharmacologic therapy of extrapyramidal motor disturbances he is concerned chiefly with those forms which belong to the amyostatic symptom complex, that is to the anomalies of the tonus. The fact that the motility disturbances, hyperkinesias and compulsion movements are hardly at all influenced suggests that the limited success of therapeutic measures is due not so much to etiologic as to localization and to physiologic differences. It is known that morphologic changes in the substantia nigra and the striatum are the anatomic foundations of those tonus disturbances which are found in some of the extrapyramidal diseases, the so-called amyostatic syndrome. However, the localization of the tonus centers does not completely explain the nature of this syndrome. When the reactive organ, the muscle fiber, is considered it becomes evident that among other factors the colloidal condition of the sarcoplasm plays a part in the maintenance of the tonus. The clinical aspects of the amyostatic symptom complex indicate that not only the sympathetic but under certain conditions also the parasympathetic plays a part in tonus regulation. The drugs generally used in the therapy of the tonus disturbances exert a paralyzing effect on the parasympathetic. Extracts of the root of belladonna have been found to have therapeutic advantages over pure alkaloids, and to explain this superiority of the root extracts it has been suggested that it contains associated substances not detectable by chemical analysis. It must also be considered that the alkaloids and the apo-alkaloids of belladonna root have a peripheral and a central point of action. The author thinks that the peripheral point of attack is not sufficiently considered in the pharmacotherapy of tonus disturbances. He describes the mode of administration of extract of belladonna root which is employed at his clinic and discusses the selection of cases, pointing out that he uses root extracts only in cases in which the amyostatic syndrome (rigor akinesia) predominates. He found extract of belladonna root particularly effective in posttraumatic akinesia and in the posttraumatic disturbances of the sympathetic regulation. The latter, like sympathetic symptoms that accompany chronic encephalitis, are the manifestation of a lesion of the brain stem.

#### Vestnik Khirurgii, Leningrad

59:443-552 (May) 1940. Partial Index

- \*Pathogenesis of Postoperative Pulmonary Complications. K. A. Shchukarev.—p. 443.
- Rectal Narcosis with Barbiturates. N. I. Popkov.—p. 454.
- Rupture of Liver. A. M. Patrik.—p. 457.
- Mechanism and Symptoms of Subcutaneous Traumatic Rupture of the Spleen. A. N. Tsirov.—p. 460.
- \*Arteriography in Obliterating Thrombo-Angiitis. E. G. Tetelbaum.—p. 464.
- Bilateral Hip Dislocation. E. I. Tsvetkova.—p. 475.

**Pathogenesis of Postoperative Pulmonary Complications.**—Shchukarev presents an analysis of 600 instances of postoperative pulmonary complications. Seventy-five per cent of the operations were performed under local anesthesia. Inhalation anesthesia no longer appears to be a contributing cause. Pulmonary embolism is a rare occurrence after operation and has no relation to postoperative pneumonia. There were 15 cases of pulmonary embolism and 2 fatal instances of embolism of the main trunk of the pulmonary artery, a total incidence of 2.5 per cent. The concept of minute embolisms advanced by the American authors Wharton, Pearson, Cutler and Hunt is hypothetical and is not supported by facts. Late occurrence, blood in the sputum and onset with pleural pain are not characteristic of postoperative complications. Existing pulmonary lesions before the operation are not the determining factor for the great majority of the cases. Exogenous factors, such as grip epidemics, undoubtedly play a role. Bacteriologic study of the sputum in 67 cases revealed the presence of pneumococci in 58.

In 41 these were of type IV. Coryllos, and Henschen of Switzerland, obtained much the same results. About 80 per cent of all postoperative pulmonary complications take place after abdominal operations. Certain alterations take place in the respiratory physiology following abdominal operations, namely interference with the diaphragmatic excursions, hypoventilation of the bases of the lungs, alteration of the bronchial tonus, lowering of the ciliary function of the bronchial epithelium, and suppression of cough. Interference with bronchial drainage results in retention of the secretions and of the bacteria. The respiratory tract of man contains in the normal state a mixed bacterial flora with the preponderance of the pneumococcus group IV. Infectious bronchitis plays the most important part in obstruction of the bronchi. The author regards atelectasis as a secondary result of bronchial obstruction and not the primary cause of pneumonia. The main factor in his opinion is defective bronchial drainage. The classic picture of massive collapse as described by Coryllos is not a frequent occurrence. Diffused bronchitis is the basis on which develop postoperative pulmonary complications. These take place most frequently in the right lower lobe. Roentgenologic studies of 47 patients before and after operation revealed a raised and immobile right diaphragm. The shift of the cardiac shadow to the involved side was observed in 6 cases; in only 1 case was the characteristic picture of massive collapse present. The mortality rate amounted to 5.9 per cent. Necropsy invariably revealed the typical picture of bronchitis and of focal bronchopneumonia of the lower segments of the lungs. Massive collapse was present in 1 of 52 necropsies. Respiratory exercises, inhalation of oxygen and use of morphine in the postoperative period are urged as prophylactic measures. Bronchoscopic aspiration as advocated by Jackson is the most rational measure in threatened massive collapse or threatened pneumonia.

**Arteriography in Thrombo-Angiitis Obliterans.**—Tetelbaum employed arteriography in 31 cases of obliterating thrombo-angiitis. The method permitted him to determine the degree of narrowing of the arterial lumen, the localization of the constriction and the state of the collaterals. The level of the thrombosing process and the degree of the development of the collateral circulation are best determined by arteriography. It makes it possible to substitute in some of the cases a sympathectomy for amputation. When amputation is indicated arteriography will, on the one hand, suggest a lower level and, on the other, it will prevent too low amputation. The author urges recourse to arteriography in cases of difficult differentiation between functional and organic disease of the blood vessels.

#### Nordisk Medicin, Gothenburg

7:1483-1526 (Sept. 7) 1940. Partial Index

- \*Sulfathiazole Treatment in Pneumonia: Blood Concentration and Elimination. A. R. Frisk.—p. 1483.
- \*Experiences Concerning Clinical Course and Later Power of Conception in 255 Cases of Extra-Uterine Pregnancy. J. Haffner.—p. 1488.

**Sulfathiazole Treatment in Pneumonia.**—Frisk reports 17 cases of acute pneumonia in which sulfathiazole was administered. There was prompt recovery without complications in 14, serous pleural effusion developed in 2 and 1 case was fatal. Toxis dermatitis occurred in 2 cases. There was no injury to blood or kidneys. Sulfathiazole is absorbed more rapidly and more completely than sulfapyridine. An initial dose of 4 Gm. is recommended, with 4 Gm. after four hours and then 1.5 Gm. every four hours until the temperature remains normal. An average concentration of 5.5 mg. per hundred cubic centimeters of total sulfathiazole and 4.5 mg. per hundred cubic centimeters of free sulfathiazole is thus maintained. This blood concentration gives the desired therapeutic effect. Nausea and vomiting are milder and less frequent than after sulfapyridine.

**Extra-Uterine Pregnancy and Future Conception.**—A follow-up of 255 cases convinced Haffner that the conservative procedure in operative treatment of extra-uterine pregnancy is justified. Although extra-uterine pregnancy recurred in 10.5 per cent of these cases, this was more than outweighed by the fact that later intra-uterine pregnancy occurred in 43 per cent. The mortality in operation for extra-uterine pregnancy is low and the danger of postoperative complications slight.

## Book Notices

**An Anatomical Analysis of Sports.** By Gertrude Hawley, M.A. Cloth. Price, \$3. Pp. 191, with 97 illustrations. New York: A. S. Barnes & Company, 1940.

This book has been prepared to fill a gap which in many cases seems to exist between the fundamental sciences offered to professional physical education students and the sports technic or methods courses which they study. It should give the prospective teachers and coaches of athletics a more definite idea of the parts which the sciences of anatomy, physiology, physics and chemistry should play in physical education. The author hopes that the book will provide an anatomic and physical basis for the selection of certain athletic "forms" such as the tennis strokes, hockey technic and diving, the adaptation of the athletic programs to individual needs and promotion of a better understanding of mechanical and physiologic factors underlying many of the injuries which occur in athletics. A chapter then takes up the functions of the various joints in detail and another one is devoted to muscular action. The rest of the book contains a detailed consideration of the various sports activities, as archery, baseball, basketball, tennis, equitation, field hockey, football, golf, swimming and diving, track athletics and winter sports. There is first a general description, then an analysis of the different motions, with a description of the muscles and joints used and the individual motions involved. In the sports with which the authoress is unfamiliar, advice is given by an expert. Finally an appendix lists the different motions made in the body and limbs and the muscles involved in each motion. The book is well written and edited. The illustrations are clear, instructive and well done. This book should be recommended for the library of all those who teach or coach athletics or are interested in physical education.

**Gynecological and Obstetrical Pathology with Clinical and Endocrine Relations.** By Emil Novak, A.B., M.D., D.Sc., Associate in Gynecology, The Johns Hopkins Medical School, Baltimore. Cloth. Price, \$7.50. Pp. 496, with 427 illustrations. Philadelphia & London: W. B. Saunders Company, 1940.

Emil Novak is America's best gleaner of the world's literature on gynecology, particularly gynecologic pathology in its relation to clinical gynecology. He has devoted the major portion of his professional lifetime to the Laboratory of Gynecological Pathology of Johns Hopkins Hospital and emphasizes his belief that the full import of the subject of gynecologic pathology can be imparted only by correlating it intimately with clinical gynecology. Novak's book justifies his belief; in presenting pathology with its clinical interpretation in mind he has created a textbook which is excellent for students, practitioners, specialists and pathologists. He might, however, emphasize that there are intricate details and unexplored fields beyond common knowledge. His book is excellent for the general pathologist but perhaps his preface might have left unsaid "for the pathologist in this particular field"; his sound and useful and meritorious work is scarcely adapted to impart knowledge to specialists in gynecologic pathology. The text is clear and comprehensive and contains most known facts except for rare observations. Most of the microscopic illustrations are good and the reproductions are praiseworthy. The macroscopic pictures are taken largely from other books, but they have been well selected. Lesser flaws may be pointed out: Thus figure 36, supposedly the wall of a Gartner duct cyst of the vagina, presents a mucous epithelium, contrary to accepted belief and Novak's own teaching. Again, pseudopapillary changes of the epithelium in some cases of hyperplasia of the endometrium do not warrant the appellation "tubal type of endometrium" (fig. 123). More important, in integration of clinical and laboratory pathology the author might have added a pathologic feature of clinical moment had he discussed obstructed drainage from the uterus and its complications—hydrometra, pyometra and metaplasia of the endometrium. A survey of this excellent work would be inadequate, indeed, without directing special attention to the chapters on the endometrial cycle, carcinoma of the cervix and the ovarian tumors—the last named a special province in which Novak's own contributions are well known. More than passing comment is merited by

Hellman, who contributes an excellent chapter on abnormalities and diseases of the placenta and appendages other than hydatidiform mole and chorionepithelioma. The tenacious and indefatigable labor of Novak reaches a culmination in this book. Surely it deserves to be widely used as a textbook and merits a prominent place on the study table of every student and practitioner of gynecology.

**An Introduction to Materia Medica and Pharmacology.** By Hugh Allister McGulgan, Ph.D., M.D., Professor of Materia Medica, Pharmacology and Therapeutics, University of Illinois College of Medicine, Chicago, and Robert Allister McGulgan, M.D., C.M., with Elsie E. Krug, B.S., R.N., Science Instructor, St. Mary's School of Nursing, Rochester, Minn. Second edition. Cloth. Price, \$3.50. Pp. 871, with 77 illustrations. St. Louis: C. V. Mosby Company, 1940.

The second edition of this textbook based on Brodie's "Materia Medica for Nurses" provides an introduction to materia medica and pharmacology which incorporates the recent advances in the subject. The opening chapter, by Elsie E. Krug, on the nurse's opportunities to learn pharmacology in the hospital ward lays down sound principles which could be read with profit by medical students as well. Users of this book will have difficulty arising from the arrangement of the subject matter and carelessness in the use of titles and subtitles, a circumstance which limits its value as a reference book. Alcohol, for example, is discussed under the chapter on drugs which act on the peripheral nerve endings. Although in general drugs are grouped in relation to the physiologic system with which they are most prominently associated, not infrequently the authors have failed to group together drugs having a common action; thus the main discussions of physostigmine, prostigmine and pilocarpine are scattered, and, when one attempts to locate acetylcholine, the index guides one to a brief mention of the substance in a section on plant hormones. In the chapter on drugs acting on the central nervous system, atropine is discussed under the subheading "Caffeine." The subject matter is broadly and adequately treated, and it will serve as a satisfactory introduction to an important field in the nurse's curriculum. Many students do not have the background to profit by so advanced a treatment, but to those who are equipped this textbook cannot fail to provide excellent insight into the essentials of pharmacology and materia medica.

**Fetal and Neonatal Death: A Survey of the Incidence, Etiology, and Anatomic Manifestations of the Conditions Producing Death of the Fetus in Utero and the Infant in the Early Days of Life.** By Edith L. Potter, M.D., Ph.D., Instructor in the Department of Obstetrics and Gynecology, The University of Chicago, Chicago, and Fred L. Adair, M.D., Professor and Chairman of the Department of Obstetrics and Gynecology, The University of Chicago. Cloth. Price, \$1.50. Pp. 207, with 31 illustrations. Chicago: University of Chicago Press, 1940.

Programs to reduce infant mortality must take into account particularly the prevention of neonatal deaths. Studies thus far published indicate clearly that the factors responsible for neonatal deaths in many instances also contribute to fetal mortality. This book, which is a survey of the incidence, etiology and anatomic manifestations of the conditions producing death of the fetus in utero and the infant in the early days of life, should aid materially all those who are interested in the prevention of fetal and neonatal deaths. It contains descriptive material relative to the technic of necropsy of the fetus and newborn infant, statistics, means of prevention and particulars of investigations. The book is excellently prepared and may be highly recommended to all those interested in this field.

**First Aid and Ambulance for Factories.** Home Office Welfare Pamphlet No. 4. Fourth edition. Paper. Price 30 cents; 1s. Pp. 36 with illustrations. New York: British Library of Information; London: His Majesty's Stationery Office, 1940.

Occupiers of factories in Great Britain are instructed by means of this pamphlet about the makeup and location of first aid boxes, instruction of workers in first aid technic, construction and equipment of dispensary facilities in factories, the value of good accident records and the importance of setting up the system under medical guidance. Samples of forms used for recording accidents are included. The varying requirements of factories of various sizes are recognized, and suitable recommendations are made regarding necessary supplies and floor plans for the accident rooms.

**Birth Control in a Midwestern City.** By Regine K. Stlx. Reprinted from the Milbank Memorial Fund Quarterly, Vol. XVII, No. 1, 2, and 4, January, April and October 1939. Paper. Various pagination, with illustrations. New York: Milbank Memorial Fund, [n. d.].

The author of the three papers reprinted by the Milbank Memorial Fund has made a careful analysis of data from the records in the files of the clinics for birth control operated under the direction of the Cincinnati Committee on Maternal Health. More than 90 per cent of the women had made some attempt to limit their families before their first visit to the clinic and the proportion of couples using contraception increased steadily as marriage lengthened. Before attending the clinic it was found that couples on relief had used contraception for less than 65 per cent of exposures, self-supporting manual workers 75 per cent of exposure and white collar workers more than 85 per cent. Pregnancy rates when contraception of some type was used were significantly lower than when none was used, but the differences were not great. Prior to admission to the clinic these rates were much lower following the use of the condom than after any other method of contraception. The preclinic contraception of those on relief was found to be ineffective, while that of those employed was relatively effective. Illegal abortion was most common among white collar workers, while spontaneous abortion was approximately the same in all groups. An occlusive rubber diaphragm and spermicidal jelly were prescribed for 98 per cent of the women who sought contraceptive advice. At the time of the follow-up only 40 per cent of those interviewed were still using this method of contraception, many having returned to the method used prior to visiting the clinic. It was estimated that all contraception, after clinic attendance, was 85 per cent effective in preventing pregnancies that would have been expected had contraception not been used. "The dominant factor associated with the acceptability of the contraceptives prescribed by the clinic was the degree of crowding in the home. . . . One third of the women who rejected the diaphragm and jelly gave as their reason the difficulty of returning to the clinic for new supplies. Nearly half of those who gave up the prescribed contraceptives did so because the diaphragm was uncomfortable, difficult to place, esthetically unacceptable or too much trouble to use. Only 9 per cent of the women who discarded the clinic prescription did so because of its failure to protect against pregnancy." This report with its numerous tables is fair in its conclusions and should be carefully studied by those who are interested in the problem of contraception.

**Diabetes: Practical Suggestions for Doctor and Patient.** By Edward L. Boritz, A.B., M.D., F.A.C.P., Associate Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia. With a foreword by George Morris Piersol, B.S., M.D., F.A.C.P., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania. Second edition. Fabrikoid. Price, \$2.50. Pp. 296, with 16 illustrations. Philadelphia: F. A. Davis Company, 1940.

The second edition of this primer has been modernized after four years chiefly by a revision of the portions devoted to the actions and uses of insulin and protamine zinc insulin. In other respects it remains an expanded and somewhat more elaborate variation of the original edition.

Beginning with a simple, eloquent and straightforward discussion of the physiology of diabetes and nutrition suitable for lay consumption and comprehension, the text becomes somewhat involved and scientific, particularly in the sections devoted to diabetes in children and to acidosis. Those sections dealing with complications (pregnancy, surgery, dental care and care of the feet) are valuable. Detailed instructions as to insulin adjustment are sound and useful. The author's method of diet calculation and instruction, converting a quantitative system into one of household measures, seems complex in attempting simplicity. Practical hints by the dietitian concerning the marketing of food and its preparation, and recipes for palatable combinations is one of the most helpful in print. There is frequent repetition of identical material in various chapters contributed by different authors.

Undoubtedly there is a place for a primer for diabetic patients and this is a good one despite its relatively minor faults. For the patient in the author's practice, trained by his methods particularly as to diet, it serves as a valuable reference and expanded source of instruction. For the diabetic population at large, more scholarly and consistent primers are available and

preferable. For the physician and student, more complete and detailed treatises on diabetes are essential.

One finishes a study of this volume with the feeling that if it had been designed for the patient alone it would have been more suitable. In its entirety it is too complex even for the intelligent layman and yet too incomplete for the average physician. It will probably remain a convenient reference book for the patients in the author's own practice, though much of it is not necessary nor easily understood by those patients.

**Statistical Methods for Medical and Biological Students.** By Gunnar Dahlberg, M.D., LL.D., Professor at the University of Uppsala, Uppsala. Cloth. Price, \$2.75. Pp. 232, with 13 illustrations. New York: Interscience Publishers, Inc.; London: George Allen & Unwin Ltd., 1940.

It seems strange that the last three years have witnessed the publication of so many books on statistical methods for the use of students of medicine and biology. The answer must be that a new need or at least a new recognition of an existing need has arisen. This book, compiled by the head of the Swedish State Institute for Human Genetics and Biology at Uppsala, Sweden, is announced in the preface as an attempt "to present statistical methods in a form calling for no special knowledge of mathematics" but at the same time to give an idea of the concepts on which these methods are based. Perhaps elementary mathematical knowledge is more extensive in Sweden than in this country, but unfortunately the average medical reader here will have great difficulty with most of the mathematical presentation. This book, in common with most others in the field, illustrates the great desirability of implementing scientific and medical educations with formal instruction on the use of the statistical method.

**Tuberculosis and Genius.** By Lewis J. Moorman, M.D. Cloth. Price, \$2.50. Pp. 272, with 10 portraits. Chicago: University of Chicago Press, 1940.

Again and again physicians have given thought to the possibility that illness, such as tuberculosis or even dementia paralytica or starvation or some other physical factor, might stimulate mental activity or even be an important factor in the production of genius. There has been, for instance, evidence to show that a crippling handicap may serve as an important factor in the development of ambition. Indeed, articles have been published to indicate that allergic children are brighter than nonallergic. In this book Dr. Moorman discusses the effects of tuberculosis as they modified the lives of a number of extraordinary workers in the field of letters. Obviously, a similar study might be made in relation to art, architecture, medicine or some similar activity. There are some who insist that tuberculosis acts particularly as a stimulus to the brain in the case of writers and that it has some special effect on the imagination. It is not possible on the basis of Dr. Moorman's writings to answer the question positively. He is inclined to believe, however, that the effects are compensatory efforts on the part of the patient to meet the insistent demands of a dread disease, to defeat the annulling vision of approaching death and, in some, to disguise a consciousness of the dismal truth. His presentation of tuberculosis as a factor in the lives of such geniuses as Robert Louis Stevenson, Schiller, Shelley, Keats and Katherine Mansfield is a document of exceptional interest, beautifully printed by the University of Chicago Press and well worthy of a place in the library of every physician.

**A Textbook of Laboratory Diagnosis with Clinical Applications for Practitioners and Students.** By Edwin E. Osgood, M.A., M.D., Associate Professor of Medicine and Head of the Division of Experimental Medicine, University of Oregon Medical School, Portland. Third edition. Cloth. Price, \$6. Pp. 676, with 37 illustrations. Philadelphia: Blakiston Company, 1940.

This is one of the better known and more complete general textbooks on laboratory diagnosis. It is particularly suitable to the need of the student or of the practitioner who needs an authoritative reference work for his infrequent departures from the simple basic laboratory routine. Dr. Osgood has been deprived by death of the collaboration of Howard D. Haskins, who collaborated in the first edition and to whom the present edition is dedicated. The spirit of the text is unchanged, however, and sixty-eight pages have been added. Of particular interest and potentially of great usefulness is a forty-six page

index by diseases. Here is an alphabetical list of diseases from abortion to yellow fever, with suggestions as to the proper laboratory work, when the condition is diagnosed or suspected, arranged in the order of significance. The author's interest is reflected in the section on hematology, which is the best one of the book. By the same token, the various discussions of the clinical application of laboratory methods to the diagnosis of syphilis are somewhat inadequately treated. There is an excellent general index and a working bibliography. The book is to be highly recommended.

**Diagnostische Drüsenpunktion.** Von Dr. R. Stahel, Assistent an der Medizinischen Poliklinik Zürich. Boards. Price, 7.80 marks. Pp. 66, with 30 illustrations. Leipzig: Georg Thieme, 1939.

While lymph gland puncture is not a new diagnostic procedure, few clinics employ the method as a routine and only a few published reports of the diagnostic possibilities have appeared in American literature. This concise monograph is an excellent survey of the subject. The author reviews the historical development of the procedure, its precise technic and method of staining of the cells, the advantages and disadvantages over biopsy, the cellular picture in puncture or aspiration of normal glands and the pathologic changes in disease. The text is beautifully illustrated with accurately reproduced photomicrographs of smears of puncture material in normal and pathologic conditions. The descriptive material is concise but adequate. At the end of the monograph is a plate of normal and pathologic cells in colors. The bibliography is carefully chosen and is pertinent. The material is carefully edited and the subject is presented with scholarly scientific restraint. The monograph will be of special interest to pathologists and hematologists.

**The Treatment of Wound Shock (Instructions Produced in Co-Operation with the Army Medical Service).** Medical Research Council: Committee on Traumatic Shock and on Blood Transfusion. War Memorandum No. 1. Paper. Price, 10 cents; 4d. Pp. 20, with illustrations. New York: British Library of Information; London: His Majesty's Stationery Office, 1940.

This short and excellent manual on the treatment of shock was prepared by the Medical Research Council in cooperation with the army medical service of Great Britain. In the eight pages of the text the mechanism, the clinical recognition and the treatment of wound shock are considered. A description of the treatment includes brief discussions of the relief of pain and restlessness, the combating of fatigue and cold, the arrest of hemorrhage and plasma loss, the restoration of the blood volume, the relief of dehydration and the administration of oxygen. There is a brief discussion of the substances which may be used for restoring the blood volume and it is concluded that human plasma and serum, because of superior keeping qualities, are more convenient than whole blood for use under field conditions. In addition the manual contains a supplement in fine type, and the following procedures are described and illustrated: (1) the army transfusion outfits and instructions, (2) the London and home counties blood transfusion outfit, (3) methods for continuous drip blood transfusions and intravenous infusion, (4) the reconstitution and administration of dried serum and plasma, (5) the administration of oxygen with the Boothby mask and (6) the composition of solutions.

**Should Married Women Work?** By Ruth Shallcross for the National Federation of Business and Professional Women's Clubs. Public Affairs Pamphlets No. 49. Paper. Price, 10 cents. Pp. 31, with illustrations. New York: Public Affairs Committee, Inc., 1940.

Married women have always worked. When the tasks moved to the factory and to the office, married women followed them. The depression greatly increased this movement. In 1890 one out of twenty-two married women worked outside the home, but in 1940 the rate is one out of five or six. Among the well-to-do women (who are the ones most opposed in objection to married workers) "there is a lower birth rate than among women in the low income brackets, many of whom are forced to work outside the home. . . .

"High infant mortality rates occur most frequently among working mothers in low-income levels where the birth rate is also high and where married women are forced to do their own housework as well as do hard work in factories or in domestic service. . . .

"Thus the babies whose mothers were employed away from home beginning when the baby was less than 2 months old had a mortality three times the average, and those whose mothers began such work when the baby was between 2 and 9 months old had a mortality about twice the average."

**Pseudo-Ischromatic Plates for Testing Color Perception.** Cloth. Price, \$9. 46 Plates. Southbridge Massachusetts: American Optical Company, 1940.

This consists of a paneled folder containing forty-six charts of the general type devised by Ishihara but presenting many improvements, evident only after a comparative test on the same subjects. The panels are not numbered and are so arranged that any desired pair may be exhibited alone and in any order. These provisions will facilitate the detection of malingerers. Inserted in a pocket in the folder, which is of substantial construction, is a pamphlet giving a brief discussion of color blindness, description of types, and instructions for making the tests and interpreting the results. There is also a brief bibliography and a tabular key for interpreting each plate. Most of the plates are applicable only to red-green defects, but there are several especially designed for the detection of blue-yellow defects. On the whole the equipment makes possible a somewhat more comprehensive examination but the technic is greatly simplified as compared to some of the other devices that have been used.

**Manual of Fractures, Dislocations and Epiphyseal Separations.** By Harry C. W. S. de Brun, M.D., F.A.C.S., Adjunct Professor of Surgery, New York Polyclinic Medical School and Hospital, New York. Cloth. Price, \$5. 468, with 150 illustrations. Chicago: Year Book Publishers, Inc., 1939.

For any surgeon who has to deal either occasionally or often with traumatic practice, this manual offers a clear, concise outline of the various methods used for the particular injury encountered. Its descriptions are briefly and intelligently stated, yet the work is detailed enough to be comprehensible. The author, who has had a long and varied experience in fracture surgery, does not leave the reader wanting for the method which is most likely to succeed. One is able to find without difficulty the described method which the author has found to be most useful in his own practice. The book itself is divided into four parts. Part I considers the treatment of fractures from a general point of view, discussing emergency and eventual treatment. Part II deals with specific fractures, including fractures of the face and the epiphyseal separations. Part III discusses dislocations, while part IV offers significant adjunctive procedures to be followed in this important and modern branch of surgery. The author is to be congratulated on obtaining the services of Dr. Richard Kovacs in the chapter on physical therapy and those of Dr. Morris Kaplan in the chapter on roentgenology. The little book is well worth the investment.

**El libro del hospital moderno.** Compilado y editado con el fin de servir a médicos, cirujanos, administradores y demás personal facultativo y directivo de hospitales. Edición de 1940-41. Board. Price, \$2.50. Pp. 426, with illustrations. Chicago: Modern Hospital Publishing Co., Inc., 1940.

First edition 1940-1941 written entirely in Spanish, it is modeled after the Modern Hospital Yearbook, to which it is similar in content and arrangement. This work is intended for use in the Latin American countries. It contains 160 pages of hospital information and suggestions and 264 pages of advertising.

**Principles of Orthopedic Surgery.** By James Warren Sever, M.D., Assistant Professor of Orthopedic Surgery, Harvard Medical School, Boston. Third edition. Fabrikoid. Price, \$3.25. Pp. 418, with 224 illustrations. New York: Macmillan Company, 1940.

Dr. Sever has thoroughly revised his concise volume covering all phases of orthopedic surgery. It is well written in a clear, direct manner and is illustrated with numerous photographs and drawings of classic pathologic entities. His discussions of diagnosis are to the point. Treatment is presented with conservatism and operative methods are in good balance. Although this book will hardly serve as a reference book for the operating orthopedic surgeon, it will be of great usefulness to the pediatrician especially and to medical students and nurses in this field of surgery.

## Queries and Minor Notes

THE ANSWERS HERE PUBLISHED HAVE BEEN PREPARED BY COMPETENT AUTHORITIES. THEY DO NOT, HOWEVER, REPRESENT THE OPINIONS OF ANY OFFICIAL BODIES UNLESS SPECIFICALLY STATED IN THE REPLY. ANONYMOUS COMMUNICATIONS AND QUERIES ON POSTAL CARDS WILL NOT BE NOTICED. EVERY LETTER MUST CONTAIN THE WRITER'S NAME AND ADDRESS, BUT THESE WILL BE OMITTED ON REQUEST.

### DERMATITIS IN FRUIT HANDLERS

**To the Editor:**—In a large orchard it is the custom to pick all the apples on the tree, the poorer grades being peeled, cored and sliced, then dried. These apples have been sprayed with lead arsenate spray (0.375 per cent) three times. After being picked, all apples are washed in soapy water, silicate solution, hydrochloric acid solution and twice in cold water. They then come out on a table and are sorted. The bruised and partly spoiled apples are used to make dried apples. These apples come down a chute, are picked up by the operator and thrust on a machine which peels the apple and cores it. This is piece work. These workers are exposed to apple juice ten hours a day and frequently cut themselves on the sharp knives. The skin irritation and small cuts are painful and exceedingly slow in healing and are described as intractable. Because of the moving parts the wearing of any type of glove would be dangerous. Neither R. Prosser White nor Schwartz and Tulipan give any suggestion for treatment or prevention in their books. I would appreciate any information you can give me with regard to prevention or treatment.

M.D., Idaho.

**ANSWER:**—Dermatitis is quite common among workers handling fresh fruits and vegetables of any kind. It seems to be caused by maceration of the skin from continuous exposure to the juices as well as by the irritating action of the juices on the skin. In the large canneries in California the workers exposed to these juices wear rubber gloves, and although they work around machinery and moving knives these are so safeguarded that accidents from the gloves being caught in the machinery are exceedingly rare. Close fitting rubber gloves reaching well above the wrist, over which are worn sleeves of an impermeable material such as described by Schwartz, Warren and Goldman (*Clothing for Protection Against Occupational Skin Irritants*, *Pub. Health Rep.* 55:1158 [June 28] 1940) would prevent the worker from coming in contact with the skin. A long apron made of similar material would prevent the juices from soiling the clothes.

If the workers object to the rubber gloves being worn next to the skin, there are now available on the market rubber gloves which are fabric lined.

If the dermatitis is severe, the treatment consists in removing the patient from work and applying mild lotions or ointments, depending on the type of dermatitis present. Lotions should be applied to the oozing, vesicular types of dermatitis and ointments to the drier types. Lotions suggested are boric acid, calamine and tannic acid from 2 to 5 per cent; ointments suggested are boric acid, Lassar's paste and zinc oxide.

Those workers having mild cases of dermatitis should be given mild ointments to apply to the parts affected and protective clothing such as sleeves and gloves and allowed to continue work while under treatment. They often recover under this type of treatment and after recovery do not usually have any recurrences. In "Skin Hazards in American Industry, Part III," U. S. Public Health Bulletin 249, page 9, appears a description of dermatitis preventive measures in canning plants, which will also apply to the case in question. See also Schwartz, Louis: Cutaneous Hazards in the Citrus Fruit Industry, *Arch. Dermat. & Syph.* 37:631 (April) 1938.

### HYPERTENSION IN FAMILY GROUP

**To the Editor:**—Recently I treated a man aged 42 who had had high blood pressure for at least fourteen years. His blood pressure was over 300 systolic, his heart was enlarged, his kidneys were affected and he suffered severely from headaches and dyspnea. He developed generalized edema and died. The deaths of two of his brothers, his father and one of his father's brothers were similar and all died young. He has five children, the oldest aged 15. I have found out since I treated this man that the three boys of his five children already have hypertension. Their ages are 7, 12 and 15, and all have blood pressures over 150 systolic; one is 175. All have albumin in the urine and all have dyspnea on exertion and frequent headaches. What can be done for these children?

L. A. Crowell, Jr., M.D., Lincolnton, N. C.

**ANSWER:**—One rarely observes such a striking example of the familial factor in the etiology of hypertensive arterial disease as that revealed by the family described. Though it is extremely difficult to differentiate clearly those influences which are purely hereditary in the biologic sense (defective germ plasma) and those which arise from familial environment in childhood, it is most important to attempt an evalua-

tion of the relative importance of the two sets of factors. The hereditary transmission of a high degree of vulnerability of the vascular apparatus of these children is irrevocable; there is nothing one can do about it. Etiologic factors acquired postnatally through environmental exposure may be amenable to correction. Dietary habits, emotional characteristics and habits of hygiene are acquired in early childhood through imitation of parents. These may sometimes be altered.

In trying to differentiate the etiologic factors in the present problem it would be useful to know something of the family history as regards hypertension on the maternal side. Should hypertensive disease be prominent there also, the prognosis for these children would be distinctly darkened. Careful inventory of their habits of life is desirable; the abuse of condiments, habitually inadequate fluid intake, habits involving insufficiency of sleep and mental attitudes of excessive apprehension are characteristics tending to provoke hypertension in vulnerable individuals. Of great importance is the question of possible familial transmission of infection with organisms showing tissue specificity for the renal parenchyma. This appears not unlikely in view of the evidences of renal injury in the children and their father. Instances of familial nephritis, transmitted through upper respiratory tract infection with streptococci are not unusual, especially if careful search is made. Rheumatic heart disease likewise is not unusual in several members of a family and over several generations; the organisms causing the tonsillitis in the parents sooner or later are likely to cause a similar infection in the children.

An excellent summary of the modern treatment of hypertension is given by Stroud (*The Diagnosis and Treatment of Cardiovascular Disease*, Philadelphia, F. A. Davis Company, 1940). The renal functional capacity of these children should be carefully evaluated. Probably therapy directed toward improvement of the renal function would be more effective than any other. One most frequently neglected aspect of treatment is the anemia so common in severe hypertension with or without nephritis. The pallor, headaches and undue dyspnea mentioned suggest that anemia may be a prominent feature. At best the outlook for these children is doubtful.

### EFFECT OF RADON SEEDS FOR URETHRAL CARUNCLE

**To the Editor:**—Have radon seeds ever been known to produce burns and scar tissue after therapeutic use for a urethral caruncle in women? Is it likely that an atresia of the vagina could result from such treatment assuming that the seeds were prepared by a reputable firm and the technic was well performed?

M.D., Pennsylvania.

**ANSWER:**—The formation of some scar tissue after the therapeutic use of radon seeds is unavoidable. Burns have occurred following the use of radon seeds when the technic has not been absolutely correct. In this connection it is important to distinguish between intense radiation effects and actual burns. It would be difficult to explain an atresia of the vagina as a result of a correct irradiation of a urethral caruncle with radon seeds.

### TREATMENT OF VENEREAL WARTS

**To the Editor:**—A woman aged 21, pregnant since January, acquired a vaginal infection. Later severe venereal warts developed. They are of the cauliflower type and are extensive and irritating to the external labia. The Wassermann reaction is negative. Smears have been negative for gonococci. However, the husband gives a history of past gonococcal infection. Many forms of treatment have been tried without any success including mild protein silver, silver nitrate, mercurochrome, merthiolate, silver picrate, potassium permanganate, mercury bichloride douches and soda douches. Is there any treatment for such a condition other than those mentioned? Would small doses of x-rays be indicated and safe? Would ultraviolet exposure be useful? This girl is in constant irritation and some kind of treatment should give relief.

M.D., Iowa.

**ANSWER:**—The cause of verruca acuminata, or so-called irritation of venereal warts, may be due to either gonorrheal or nongonorrheal infection. The warts are prone to be much more profuse during the period of pregnancy.

Any treatment by the use of local antiseptics is bound to fail as long as the mechanical presence of the irritating masses remains. Therefore the first step in the proper management of such cases is to remove the warts by surgery, which may be done with the knife or with a cutting current. Regardless of how removed, the base must be treated by electrocoagulation. Small warts are best removed by complete electrocoagulation without preliminary surgical removal.

Following removal by this method, local antiseptic douches will have a reasonable chance to clear up the local infection, which is the primary cause of the verrucae. Moderate doses of sulfanilamide by mouth may be of value in helping to control the infection and in preventing recurrence of the warts.



## SUPPRESSION OF LACTATION IN SCARRED BREASTS

*To the Editor:*—A woman aged 22 suffered a severe burn at the age of 4. The scar tissue extends from the umbilicus to the chin. She is now approximately seven months pregnant. The nipples are entirely destroyed and the breasts completely covered with scar tissue. What care would you suggest for the breasts and at what time should it be instituted?

D. K. Matthews, M.D., Dresden, Ohio.

**ANSWER.**—Treatment should be directed toward drying up the breasts immediately after delivery. The present method consists in the application of a tight binder to both breasts and the use of ice. The intake of fluids can be limited moderately. This regimen will limit the engorgement of the breasts, which should completely subside in seventy-two hours.

Estrogens in large doses may prevent lactation when administered during the first few days of the puerperium. The new synthetic estrogenic drugs derived from stilbene have been used experimentally for this purpose with considerable success. They are not commercially available. If a patient receives 5 mg. of stilbestrol by mouth daily no engorgement takes place, the breasts remaining soft and flaccid. The medication is usually continued for about a week. Since stilbestrol is not available, 5 mg. of estrone daily may be administered for a similar time. Some investigators have reported success in suppressing lactation by administering from 50 to 150 mg. of testosterone propionate over a period of two or three days. The endocrine therapy of this condition is obviously quite expensive at present. As is usual in estrogenic therapy, care must be exercised in its administration.

## PRIMARY OR METASTATIC OVARIAN CARCINOMA

*To the Editor:*—A white woman aged 41, a secundipara, was being treated for varicose veins. About two days after her last injection she suddenly experienced sharp lancinating pains in the lower part of the abdomen and collapsed. I was told that examination revealed rigidity, rebound and tenderness over the lower left quadrant and slight elevation of temperature. Vaginal examination revealed a sensation of mass in the left fornix. A diagnosis of pelvic inflammatory disease was made. After a few weeks of conservative therapy the patient was reexamined and a diagnosis of left ovarian cyst was made. Three weeks later, on entering the abdomen, I found some serosanguineous fluid in the pelvis. The left ovary was about 3½ inches in diameter, mainly cystic. The cystic portion ruptured during the operative procedure. There was some doubt as to the pathologic diagnosis. The right ovary appeared normal in size, shape and consistency. A left oophorectomy was done. Ten days later the pathologist's report was papillary cystadenocarcinoma of the ovary. High voltage roentgen therapy was instituted soon after her discharge from the hospital. Should the patient be operated on again for removal of the right ovary? Should the uterus be removed at the same time? Is it sufficient to inactivate the remaining ovary by roentgen therapy and keep the patient under observation?

M.D., New York.

**ANSWER.**—If the patient really has a carcinoma of the ovary, radiation therapy will not suffice to insure a cure. Recourse to reoperation is the procedure of choice, but first the pathologic specimen should be reviewed not only to make certain of the diagnosis but in search for evidence suggestive of a metastatic growth rather than a primary ovarian cancer.

At the time of reoperation the upper abdominal viscera should be palpated for a primary growth and the pelvis should be surveyed critically for evidence of extension; this pertains particularly to the affected side. If there is local extension, a unilateral radical procedure with exposure of the ureter may be indicated. In any event the remaining ovary should be removed together with the body of the uterus. Authorities differ as to whether complete removal is preferable to a supra-vaginal hysterectomy. It is agreed that the uterus should be opened immediately on removal, for the body of the uterus may be the site of a primary growth which extends to the ovary.

## INTRAOCULAR FOREIGN BODY

*To the Editor:*—A man about 47 years old was struck in the right eye by a piece of brass several millimeters in diameter. As a result of this accident he now has an intra-ocular foreign body and a large corneal scar. Otherwise the eye is normal, although no sight is present because of scar. 1. What are the chances of extrusion or removal of the foreign body? 2. What are the chances of a successful corneal transplant? 3. What are the chances of sympathetic ophthalmia? 4. Has maximum improvement taken place or may further improvement be expected either through any operation or through extrusion of the foreign body? 5. Should the eye be removed at this time?

M.D., Connecticut.

**ANSWER.**—1. The chances of extrusion spontaneously of the foreign body are nil. The possibilities of operative removal depend entirely on the location of the body, the condition of the eye and the skill of the operator.

2. There is no sense in even attempting a corneal transplant as long as there is a foreign body within the eye. After that is removed, the possibilities of a transplant may be considered and depend on how much normal corneal tissue remains.

3. There are considerable chances.

4. With the meager details at hand, it is impossible to answer this question.

5. Again the answer depends on the condition of the eye, the length of time the foreign body has been present, the duration and character of whatever inflammation may be present, and the judgment of the ophthalmic surgeon, based on experience with similar cases.

## GALACTOCELE

*To the Editor:*—A nursing mother complained of pain, tenderness and a feeling of engorgement in one breast, the symptoms becoming progressively worse over a period of about five days. Examination revealed the entire lower quadrant of the breast to be red, tender, hard and engorged, and warm to the touch. The rest of the breast was soft and normal. A breast abscess was strongly suspected and I was about to treat her for it when she pointed out to me a tiny vesicle on the nipple. This was in the lower part of the nipple and to all intents and purposes looked just like a small 2 mm. vesicle. Partly on suspicion and partly for lack of something better to do I opened this small vesicle with a scalpel. Following a tiny incision, milk gushed out in a steady stream under considerable pressure and all the symptoms disappeared. The same condition has occurred again about three times in the same breast and once in the other. I realize that one of the main milk ducts is being blocked but the obstruction is not a caking of milk but an actual overgrowth of epithelium over the duct opening. The skin which obstructs the duct is white in appearance and bulges from pressure of the milk but still seems to require incision, after which the breast is all right for a week to ten days. I have never seen or heard of such a condition. A prominent obstetrician told me that he had never heard of such a thing but advised taking the baby off the breast rather than risk a breast abscess which might follow incision.

M.D., Pennsylvania.

**ANSWER.**—Each breast is made up of from fifteen to twenty-four lobules arranged radially. The secreting acini of each lobule are connected by small ducts which unite to form a lactiferous duct, the opening of which can be distinguished as a minute orifice in the nipple. Undoubtedly the tiny vesicle which is described represents the closure of such an orifice and the resultant distention of the duct.

The collection of milk in the duct system of a lobule usually produces a reddened, tender, fluctuant enlargement at the base of the nipple and is known as a galactocoele. In the case described the distention of the duct system must have extended downward to involve the entire collecting ducts of an entire lobule, so that this lobule became reddened and swollen. Except for the lack of acute symptoms, these tender areas resemble abscesses of the breast.

Repeated incision of the lactiferous duct is likely to lead to infection. It is probably wiser to consider drying up the breast than to risk possible complications.

## EXCESSIVE IRON IN WATER SUPPLY

*To the Editor:*—A condition has arisen in the Central School about which I should like to have your opinion. The water taken from wells is heavily impregnated with iron salts. To overcome this condition a chemical with the trade name "Mogul," made by the North America Fiber Products Company of Cleveland, has been used. I understand from the engineer that this is satisfactory in the boilers but the rusty looking water if left in the bowls causes a brownish red discoloration and not only encrusts but corrodes the pipes, particularly at the joints. Information from the manufacturers advises us to put 1:1,000,000 of this liquid in the water system to overcome this difficulty. This, of course, would include the drinking fountains. I should like to know whether this would be in any way harmful, especially if used continuously. The only alternative I see is replacement of the pipes when they fill with the rustlike material or when they leak through corrosion. The water has been tested and found satisfactory for human consumption.

M.D., New York.

**ANSWER.**—On the basis of the information given it is not possible to give a satisfactory answer to the inquiry. Under the conditions cited it seems probable that the water supply from the school well not only contains excessive iron but may also have a low hydrogen ion value which makes it corrosive to pipe material and causes the staining of fixtures reported.

The use of chemicals to treat water for boiler purposes is often desirable, but it is generally unwise to use the same water for drinking purposes especially when specific information is not available concerning the chemical compound used, other than its trade name.

A physician should recommend to the school board that it employ the services of a competent water chemist to investigate the problem and give expert advice.



## PAINFUL, TENDER FINGERS IN PREGNANCY

**To the Editor:**—A primipara about a month from term has been having some swelling and tenderness of her hands which is unlike anything in my experience. It started about three weeks ago with swelling and tenderness, especially of the ends of the fingers, the thumb, the index and middle fingers and the medial aspect of the ring finger (nerve distribution). There was some pain in the same areas but it has been controlled. The patient is passing more than a quart of urine a day which is normal in color, specific gravity 1.014, reaction slightly acid. There is no albumin with either Heller's or the heat and acetic acid tests. There is no sugar. The blood pressure is 115 systolic, 55 diastolic. The pulse is 88. At first the trouble was in the right fingers and was worse when the patient got up in the morning. Gradually it wore off till she felt much better in the afternoon. There was no edema of the ankles and only a little of the feet. The patient's vision is normal. About two weeks ago the other hand became affected also. The swelling and edema of the fingers persist all day now. The ends of the fingers are so sore and tender that the patient can hardly wash her dishes. Now there is some swelling of the ankles and of the face. At first I tried having her take two yeast cakes a day but that caused no improvement, so I did not pursue the vitamins further. Then I gave her half a grain (0.03 Gm.) of phenobarbital three times a day. That stopped the pain but did not affect the tenderness or swelling. I have had her rub the fingers and hands toward the body and hold the hands up supported on pillows. That gives some relief. What can I do to relieve this patient? She is having only an occasional light headache.

Persis S. Robbins, M.D., Bradford, Pa.

**ANSWER:**—From the data presented it seems impossible to classify this condition properly. The distribution of the pain corresponds to the sensory distribution of the median nerve but it seems highly improbable that there should be disease of the two median nerves at the same time. Bilateral cervical rib would seem incapable of producing pressure on these fibers alone. There seems to be no good reason for a peripheral neuritis. The common causes for this condition are alcohol, arsenic and lead, and even these should have a more general distribution.

The symmetric character of the pain suggests Raynaud's disease but the physical examination does not seem to support this diagnosis.

A moderately severe hypothyroidism should be considered. This often appears first as puffiness about the hands and wrists and is frequently associated with tingling but seldom with acute pain. Hypothyroidism occasionally appears during pregnancy. A basal metabolism determination would be helpful.

The neuritis of a vitamin deficiency is an attractive diagnosis but seems difficult to support. If there is lack of vitamin B<sub>1</sub> the therapy must be more vigorous than the administration of two yeast cakes daily. Full doses of thiamine hydrochloride must be used over a considerable period.

It would be helpful to know whether motor phenomena exist as well as the sensory ones.

## PERSISTENT FEVER IN INFECTIOUS MONONUCLEOSIS

**To the Editor:**—My grandson, aged 5, about nine weeks ago acquired a mild nose and throat infection and had a few enlarged cervical glands. He had a fever of about a degree, and after several weeks a diagnosis of acute mononucleosis was made. This was confirmed by the heterophil blood test as well as by blood counts and blood smears. The patient has had a persistent fever varying from 0.6 or 0.8 degree to sometimes as high as 1.5 degrees. During the past six weeks he has been kept in bed most of the time and his fever still persists, although not as high as when he is active. There are absolutely no other recognizable signs. He has no enlarged spleen, his tonsils are apparently normal and roentgenograms of the chest also appear to be normal. He seems pretty well and has gained weight, although he does seem to fatigue rather easily. Several competent pediatricians have seen him and assure me that he will get well but they know of nothing to do to hasten the recovery, particularly to terminate the fever. Whatever literature I have been able to find on the subject states that the fever usually persists three or four weeks and that the disease is self limited. May I ask if there are any other measures to be adopted and also whether it is uncommon for this condition in a child to persist with fever for a period of eight or nine weeks. If you have other suggestions to offer, I should be pleased to learn them. Is sulfanilamide of any value in this condition?

M.D., Wisconsin.

**ANSWER:**—Although the fever in infectious mononucleosis usually lasts for from three to four weeks, it is not uncommon for it to last longer. There are cases in which as much as a degree of fever was present for over three months. In one case, a few tenths of a degree was intermittently present for six months. Certainly a few patients have a prolonged convalescence with a considerable disability for many months. No effective treatment is known. Sulfanilamide is probably without value. Occasionally arsenic in the form of solution of potassium arsenite given to tolerance for two to three weeks appears to be of value. General measures such as an adequate diet and vitamin intake should be observed. The patient should be kept relatively quiet.

POSSIBLE ENCEPHALITIS FROM ANTISYPHILITIC  
ARSENICAL THERAPY

**To the Editor:**—A man on whom the diagnosis of primary syphilis was made showed typical spirochetes on darkfield examination. On Sept. 17, 1940, he was given 0.45 Gm. of nearsphenamine and 0.2 Gm. of a bismuth compound. On September 24 he was given 0.6 Gm. of nearsphenamine and 0.2 Gm. of the bismuth compound. On September 26 he started showing some early symptoms of encephalitis: marked irritability, apprehension and increased deep reflexes. On September 28 he became unconscious and remained so for about one week. The spinal fluid showed no change except increased pressure. He showed no other symptoms except those of an encephalitis. He has responded well to therapy and is now recovered. The problem now is how to treat his syphilis. Should any arsenical preparation be given?

M.D., Kentucky.

**ANSWER:**—The symptoms mentioned are suggestive of hemorrhagic encephalitis. Nothing is said about opisthotonos. It could not have been due to syphilis without a great increase in the cell count and without a positive Wassermann and flocculation test on the fluid. Such hemorrhagic encephalitis usually comes on early in the course of syphilis. One would not consider the use of arsenicals in the future under any circumstances. In a situation like this it is necessary to employ bismuth therapy. Of course that would be impossible if one were to use an insoluble preparation. On that account it would be preferable to give an injection twice a week of one of the soluble salts, and iodobismutol with saligenin might be tried. It has been shown that a biweekly intramuscular injection of iodobismutol gives a sustained excretion curve of bismuth in the urine that is high enough to indicate a satisfactory therapeutic level of bismuth in the blood stream. Naturally the patient should be watched for evidence of irritation of the kidneys and for any evidence of mucous membrane irritation around the teeth. It is probably safe to carry on such therapy for months. A specimen of blood should be taken every three months and the treatment kept up until the serologic tests have been negative for one year.

## FATIGUE IN FIRE FIGHTERS

**To the Editor:**—The local forestry department has asked me several questions which I would like to refer to you. We have numerous forest fires in this section during the summer and as the altitude is high (5,000 to 8,000 feet) the fire fighters tire easily and the number of man-hours is cut down considerably. They were interested in getting something in the nature of a stimulant that would help these men to last longer in their work. The forestry department thought about having the men inhale pure oxygen from time to time. Do you think that it would relieve fatigue enough to justify its use? Can you make any suggestions along this line?

Herbert J. Schwartz, M.D., Challis, Ida.

**ANSWER:**—It is not likely that, at an altitude not exceeding 8,000 feet above sea level, anoxemia is the main factor of excessive fatigue in men fighting forest fires, provided the density and other character of the smoke do not significantly interfere with the breathing. At any rate, a five to ten minute rest in the horizontal position every hour will probably do as much as inhalation of oxygen in overcoming the "oxygen debt" developed by the intense physical exertion, and the workmen would have to cease labor in any event during the oxygen administration. Men fighting forest fires probably do more intense physical labor for longer hours than is the case in most types of ordinary physical work. Hence more rapid onset and more severe fatigue is to be expected. But if the fire fighters are also exposed to excessive heat for many hours, one must think of excessive sweating, desiccation of tissues and loss of blood and tissue chlorides. It has been abundantly shown that tablets of table salt and ample intake of water are of real value in the prevention of fatigue under such conditions. Excessive physical exertion calls for an abundance of food. If the fire fighters' meals are further apart than three to four hours sugar, in the form of candy, between meals, will undoubtedly help to delay or minimize fatigue. Sodium chloride tablets and candy are simple matters to handle, even under conditions of fighting forest fires in the Rocky Mountains. One must also bear in mind that, in the case of extensive forest fires, many persons may be drafted as fire fighters who are not by daily physical work conditioned to extreme and sustained physical exertion. Some twenty-five years ago tests with sodium phosphate given by mouth were made on soldiers in Europe, with apparent good results in reducing fatigue. The biochemical basis for this therapy is now questionable, and the fact itself is as yet so much in dispute that one cannot promise any value of a few grams of inorganic phosphate by mouth for the fire fighters. But short and frequent periods of complete rest, water, sodium chloride and candy should prove helpful.

## PROBABLE PEMPHIGUS VEGETANS

*To the Editor:*—An obese white woman in her fifties has for two years had sores on her tongue, buccal mucosa and lips. For one year she has had an eruption in the groin. The oral lesions are marked by large vesicles on the lips which break, crust and finally leave raw surfaces which bleed easily. The margins of the tongue are raw and tender and show digitations as though in contact with teeth (although the patient is edentulous). The surface of the tongue is not remarkable. The buccal mucosa is covered with scattered white vesicles and tiny raw areas, the first evidently resulting in the second. There is some thinning of the lips and a pinched appearance at the angles of the mouth but no true fissuring and no seborrhea or keratitis. This condition has been treated by others with a multitude of antiseptics, which included sodium perborate and most recently gentian violet, to no avail. The inguinal lesion began as a small papule on the genitalia, which was soon followed by new ones in the perineum, in the groins especially on contact surfaces, in the anal folds, under the breasts and, so the patient believes, in the axillae. These are painless weeping granulomas covered by thin epithelium having the cyanotic appearance of hemorrhoids but feeling firm to the touch. They are irregular, and are largely discrete with normal skin intervening. They tend to vesiculate and then weep a watery fluid, leaving a raw surface which then seems to epithelize. Under the breasts there are visible flat discolorations in the skin which represent, the patient says, sites of lesions similar to those described. There is no noteworthy lymphadenopathy and there are no sinuses. The blood Kline and Mazzini tests are negative, as is the Frei test. A smear of the oral lesions is negative for Donovan bodies. The formal-gel test is not indicative of granuloma inguinale. A biopsy has not been feasible. Massive oral doses of vitamin B complex yielding about 5 mg. of riboflavin daily plus parenteral thiamine hydrochloride given for one week simultaneously with the administration of sulfanilamide 40 Gm. daily for the week have had no beneficial effect. The patient is now receiving fuadin in the belief that she has granuloma inguinale despite the lack of confirmatory evidence. What suggestions as to diagnosis and procedure can you offer?

M.D., Indiana.

*ANSWER:*—One might keep in mind the possibility of a deficiency disease, particularly vitamin B complex, but as there has been no response of the lesions around the mouth with this type of therapy it may be eliminated. From the description it is not easy to get a picture of the whole process, but it sounds most like a chronic type of pemphigus, though ordinarily the pemphigus vegetans type of the disease is more rapid and leads to a fatal termination. The blood picture should be studied carefully to eliminate lymphoblastoma; the blood sugar should also be examined. As pemphigus vegetans is a grave disease, consultation with a competent dermatologist who would help to share the responsibility would be advisable.

## EFFECTS OF HIGH HEELED SHOES

*To the Editor:*—When I see women walking with the modern high heeled shoes I often wonder if they could cause some of the symptoms which arise in women which are hard to explain. Of course I can understand the effect it might have on the lower limbs but it seems to me that the equilibrium of the body might be disturbed. Can they cause a malposition of the pelvis or spine? Can they cause any disorder in the pelvic organs? Do the small bottoms of these long heels cause a tendency to turn over and this constant fear of turning over while walking cause nervousness or vertigo?

M.D., Pennsylvania.

*ANSWER:*—The high heeled shoe may cause an increased lumbar lordosis and a pelvic tilt. In young women this amount of tilt can be compensated for readily. In older women or people with arthritic changes this alteration of position may cause a strain and backache. It is hardly conceivable that any abnormality of the pelvic organs could be attributed to high heeled shoes. It is doubted that the instability of the high heel and small weight-bearing surface cause sufficient strain to account for any nervousness or vertigo. It is true, however, that women who walk in high heeled shoes with small weight bearing surfaces may have an altered gait and an altered posture. This altered posture when associated with fatigue and visceropostosis may be a factor in vasomotor disturbance.

## COOKING METHODS AND VITAMIN PRESERVATION

*To the Editor:*—Will you please let me know whether vitamins are preserved or destroyed in the use of the rapid pressure cooker and in the use of the slow heat fireless cooker. It would be contemplated that both meats and vegetables be cooked in these cookers if there is no appreciable loss of vitamins.

Lucius F. Herz, M.D., New York.

*ANSWER:*—The smallest possible loss of vitamin C occurs when vegetables are cooked in the new style pressure cookers which operate under a small amount of pressure. When vegetables are boiled in water, from 15 to 30 per cent of the vitamin C is transferred from the vegetable to the cooking water and 15 per cent of the vitamin is destroyed by oxidation (McIntosh, Jennie A.; Tressler, D. K., and Fenton, Faith: The Effect of Different Cooking Methods on the Vitamin C Content of Vegetables, *J. Home Econ.* 32:692 [Dec.] 1940). The use of a slow heat fireless cooker cannot be expected to retain as much vitamin C as the rapid pressure cooker

because there appears to be an enzyme present in vegetables which rapidly changes vitamin C to another substance that has no antiscorbutic properties. This action is prevented by heat.

According to recent experimental work the best way to cook meat for conservation of vitamin B<sub>1</sub> is to broil or fry it as quickly as possible. Long cooking processes, such as roasting or stewing, destroy about 50 per cent and long frying destroys 40 per cent of the vitamin B<sub>1</sub> content of meats.

## CLOSURE OF DRUM MEMBRANE PERFORATIONS

*To the Editor:*—What is the best medication to hasten the closure of a perforation in the ear drum? The patient in question was seen by a physician on Sept. 30, 1940, who reported "acute otitis media with a slight discharge through a small perforation of the right drum." On October 22 the same doctor examined the ear again and reported "no discharge. The perforation is closed and the only signs of previous inflammation are two to three small blood vessels passing to the healed portion of the drum and seen only with high magnification and a strong light." A day or two ago I examined the drum and saw two perforations, one in the posterior half about 2 mm. in diameter and a small one almost closed in the anterior half. There was no discharge and no sign of inflammation. The patient has no pain or discomfort and his hearing is only slightly impaired. He has been using phenol and glycerin drops for some time, daily, at the advice of his physician. The patient has been in the army on active duty but was relieved when this condition was discovered. He is of course doubly anxious to get the perforation closed for this reason. The history of his otitis goes back many years, when he was boxing as a boy and injured his ear and shortly after went in swimming, following which he had severe otalgia for some time. Around September 1 of this year he began having earache again and a discharge began the 3d. Sulfanilamide was used and the discharge stopped five days later. Around September 12 the discharge began again. This time the canal was irrigated with boric acid and swabbed out with silver nitrate. About the 18th the draining ceased again but resumed on the 23d, and the perforation in the anterior half of the drum was first discovered on the 25th. Sulfathiazole powder was dusted in the canal of this time, according to the patient. The first time I looked at the drum I was sure about the two perforations but the second time I was less sure. The small hole seemed to be completely closed and the larger one could have been covered by a more transparent tissue than made up the rest of the drum, by appearance. Is this probable or common? Is it sometimes possible to mistake an intact drum for one that apparently has a large definite perforation?

Hal E. Bennett, M.D., Vilas, Fla.

*ANSWER:*—Perforations in the drum membrane that do not involve more than a fourth or a third of the total area tend to heal themselves spontaneously with a thin transparent scar, which through an ordinary ear speculum may be so thin that it still looks like a perforation. By means of magnification or a speculum with air pressure attachment, such as a Siegel speculum permitting the drum to be moved in and out by air pressure, these thin scars are readily discernible.

A small perforation that does not close spontaneously may often be closed by the careful application of a minute amount of trichloroacetic acid to the margins of the perforation followed by the application of a tiny paper patch, best made from cigaret paper and moistened with 1 per cent phenol in glycerin. This treatment may have to be repeated once or twice at intervals of two or three weeks until the perforation has closed.

Both the application of the trichloroacetic acid and the paper patch requires considerable dexterity and experience with ear treatments and should not be attempted by one who is not thoroughly conversant with the ear and delicate manipulations around the drum membrane.

## STERILIZATION OF SHOES WITH FORMALDEHYDE SPRAY

*To the Editor:*—In the Oct. 5, 1940 issue of The Journal under Queries and Minor Notes, page 1215, a question was asked regarding the sterilizing of fungus-infected shoes with formaldehyde. May I suggest the following method, which is simple, effective, inexpensive and readily applicable to large numbers of shoes: An ordinary nasal atomizer is filled with solution of formaldehyde. With the tip of the atomizer well up in the toe of the shoe (the shoe lying on its side) one compression of the atomizer bulb sends a cloud of formaldehyde vapor into the forepart of the shoe. Then the tip of the atomizer is moved to the heel section of the shoe and the bulb is again compressed once, sending another cloud of vapor into the hind part of the shoe. The spraying should be performed on three successive nights. Shoes can be worn during the day. Tests have shown that it required three successive daily sprayings to effect a thorough sterilization. Shoes should not be worn until at least eight hours after spraying. As formaldehyde vapor is irritating to the eyes, the respiratory tract and the skin, the spraying should be done well away from the face of the operator, in a well ventilated room, and rubber gloves may be worn. When not in use the tip of the atomizer should be sealed with a pin, as this prevents plugging by corrosion. Further details can be found in an article by Birnbaum and White-Sweres (Simple Method of Sterilizing Fungi-Infected Shoes, *M. Bull. Vet. Admin.* 17:48 [July] 1940).

Leo Birnbaum, M.D., Downey, Ill.

# The Journal of the American Medical Association

Published Under the Auspices of the Board of Trustees

VOL. 116, No. 2

COPYRIGHT, 1941, BY AMERICAN MEDICAL ASSOCIATION  
CHICAGO, ILLINOIS

JANUARY 11, 1941

## ANGINA PECTORIS, CORONARY FAILURE AND ACUTE MYOCARDIAL INFARCTION

THE ROLE OF CORONARY OCCLUSIONS AND COLLATERAL CIRCULATION

HERRMAN L. BLUMGART, M.D.

MONROE J. SCHLESINGER, M.D.

AND

PAUL M. ZOLL, M.D.

BOSTON

Despite the rapid advance in our knowledge of cardiovascular disease, pathologic examination of the heart frequently fails to disclose the conditions which are anticipated on the basis of the clinical diagnosis. The clinical diagnosis of "coronary thrombosis" is often made but no thrombosis may be found; in other instances a fresh infarct is disclosed but no fresh thrombosis of any arteries supplying the affected area may be evident. Conversely, fresh coronary thrombosis or complete occlusions of main coronary arteries may be found post mortem but without any corresponding clinical phenomena. Because of the frequent disparities between clinical diagnoses and pathologic observations a detailed clinical and pathologic study was made in a consecutive series of necropsies. In the pathologic examination of the heart, a method devised by one of us (M. J. S.) was used,<sup>1</sup> since it affords more precise information regarding the structural changes of the coronary arteries. The results in 125 cases have been described by us.<sup>2</sup> Our purpose in the present communication is to summarize the results obtained in a more comprehensive series of 355 cases utilizing additional technics to clarify some of the problems involved. Particular attention has been directed to the structural cardiac changes and their functional significance in order to gain insight into the clinical problems associated with angina pectoris, coronary thrombosis and myocardial infarction. The importance of the collateral circulation in obviating the effects of obstruction to the coronary arteries is to be emphasized.

Owing to the lack of space, this article is abbreviated here. The complete article appears in the authors' reprints.

This investigation was aided by a grant from the Josiah Macy Jr. Foundation.

Read before the Section on Practice of Medicine at the Ninety-First Annual Session of the American Medical Association, New York, June 13, 1940.

From the Departments of Medical Research and Pathology of the Beth Israel Hospital and the Departments of Medicine and Pathology, Harvard Medical School.

1. Schlesinger, M. J.: An Injection Plus Dissection Study of Coronary Artery Occlusions and Anastomoses, *Am. Heart J.* 15:528 (May) 1938.

2. Blumgart, H. L.; Schlesinger, M. J., and Davis, David: Studies on the Relation of the Clinical Manifestations of Angina Pectoris, Coronary Thrombosis and Myocardial Infarction to the Pathologic Findings, with Particular Reference to the Significance of the Collateral Circulation, *Am. Heart J.* 19:1 (Jan.) 1940.

### METHODS

*Pathologic Methods.*—The technic used in injecting and dissecting the heart has been described<sup>1</sup> and summarized<sup>2</sup> previously and therefore will be only briefly stated here. The right and left coronary arteries were injected simultaneously with differently colored radiopaque masses under a pressure of from 150 to 200 mm. of mercury. The heart was then unrolled so that all of the coronary arteries lay in one plane and a roentgenogram was made. A complete dissection of the arteries was then carried out. Multiple representative sections of the myocardium were studied histologically. Instead of presenting colored copies of the actual roentgenograms we have prepared tracings of the coronary arterial tree of each heart.

*Chemical Methods.*—To study the effects of coronary arterial narrowing and occlusion on the myocardium, an estimate of the amount of fibrosis was made by measuring chemically the collagen content of the myocardium. This method affords a quantitative estimate of the degree of fibrosis in the myocardium. The collagen method has been described previously,<sup>3</sup> and the results obtained in a series of hearts have been reported.<sup>4</sup>

*Clinical Methods.*—Since the main purpose of this study was to understand clinical signs and symptoms more clearly and accurately, only those cases were included in which detailed clinical information could be obtained from reliable sources.

### OBSERVATIONS IN THE NORMAL HEART (I. E., HEARTS WITH LITTLE OR NO CORONARY ARTERIOSCLEROSIS OR OTHER ABNORMALITIES FROM PATIENTS WITH NO CLINICAL EVIDENCE OF CARDIOVASCULAR DISEASE AND DYING OF NONCARDIAC DISEASE)

While it was formerly believed that the coronary arteries were end arteries, it gradually has become the opinion of most investigators that communications may exist between the coronary arteries. The extent and nature of these communications, the conditions which favor their development and their functional significance are, however, still not clear. Watery solutions injected into one coronary artery are always found in the other large coronary arteries, demonstrating that even in the normal heart fine communications exist between the main coronary arteries. When, however, normal hearts were injected with the colored lead agar mass utilized in these studies, passage of the mass from one coronary artery to the other side was unusual. Since the lead agar suspension penetrates regularly only as far as arterioles 40 microns in diameter, interarterial collateral pathways of 40 microns or more may be regarded as generally absent in normal hearts. Previous studies<sup>5</sup> have demonstrated however

3. Gilligan, D. R., and Lowry, O.: A Method of Measuring the Collagen Content of Small Amounts of Muscle and Other Tissue, to be published.

4. Blumgart, H. L.; Gilligan, D. R., and Schlesinger, M. J.: The Degree of Myocardial Fibrosis in Normal and Pathological Hearts as Estimated Chemically by the Collagen Content, *Tr. A. Am. Physicians*, volume 55, to be published.

5. Schlesinger,<sup>1</sup> Blumgart, Schlesinger and Davis.<sup>2</sup>

that, if narrowing of a coronary artery occurs, these larger collateral pathways develop and supply that area of the myocardium which would otherwise suffer from diminished blood flow. Vessels of this larger size are of major importance in obviating the effects of arterial narrowings and occlusions; on the other hand, the fine interarterial coronary communications of less than 40 microns in diameter do not prevent infarctions following sudden thrombotic or embolic occlusion of a coronary

vessels large enough to be functionally significant in obviating the untoward effect of rapidly developing coronary narrowing or occlusion.

OBSERVATIONS IN CASES WITHOUT CLINICAL  
CARDIOVASCULAR DISEASE IN WHICH THE  
HEART SHOWED OLD HEALED COM-  
PLETE OCCLUSION IN AT LEAST  
ONE CORONARY ARTERY

Complete occlusion or considerable narrowing of one or more coronary arteries may exist without giving rise to any clinical symptoms or signs. Thirty-eight cases with old occlusions of the main coronary arteries or primary branches were found without related clinical signs or symptoms. Thirty-four additional hearts showed considerable narrowing, but no occlusion, of one or more of the main coronary vessels without clinical symptoms or signs of cardiovascular disease. In those cases in which electrocardiographic tracings were available the complexes were normal.

This apparent inconsistency between the presence of long standing obstructive arterial lesions and the absence of significant pathologic or clinical evidence of myocardial damage was dispelled by the demonstration of a

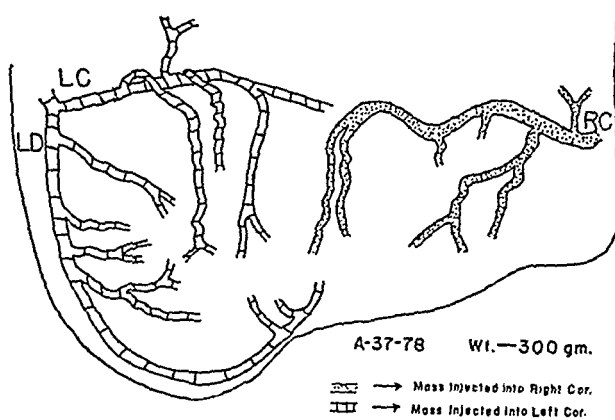


Fig. 1 (case 1).—Diagram of normal coronary arterial tree of man aged 72.

artery clinically or after experimental ligation of an artery. The collateral pathways which hitherto have attracted particular attention communicate between arteries and the cavities of the heart or between capillaries, veins and cavities of the heart. The collateral pathways demonstrated in abnormal hearts by the lead agar mass communicate between coronary arteries and therefore would appear to be more significant in the maintenance of capillary blood flow.

It was of particular interest to observe many normal hearts in this series with little or no coronary arteriosclerosis or other abnormalities in patients over 70 years of age. This indicates that the development of an anastomotic circulation is not a necessary concomitant of the aging process, a conclusion somewhat contrary to the experience of others.<sup>6</sup>

CASE 1.—A man aged 72 died of fibrosarcoma of the femur; the heart was normal and there was no arteriosclerosis or other abnormality in the coronary arteries. Figure 1 is a diagram of the coronary arterial tree.

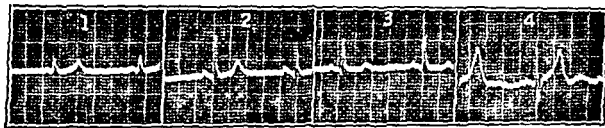


Fig. 2 (case 2).—Normal tracing one year before death.

The foregoing observations are based on a study of 149 cases which showed no clinical evidences of cardiovascular disease and in which the hearts post mortem were structurally normal in every respect. The conclusions derived from the observations in this extensive series are in accord with those recorded previously;<sup>5</sup> regardless of the age of the subject, normal hearts regularly have fine interarterial coronary communications but do not possess an anastomotic circulation of

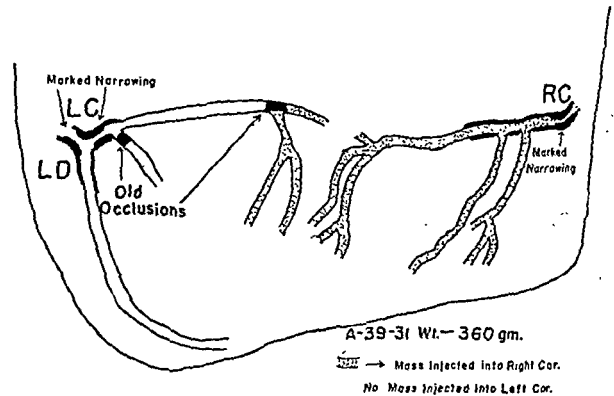


Fig. 3 (case 2).—Diagram of coronary arterial tree: unilateral injection of lead agar mass into right coronary artery.

collateral circulation in relation to the obstruction in each of these hearts. This collateral circulation was clearly demonstrated by the injection mass and, in each instance, served as a by-pass around the arterial obstruction. In some hearts the collateral pathways communicated between portions of the same artery proximal and distal to the occlusion; in other instances the artery distal to the occlusion derived its supply from distant vessels. While the collateral circulation generally safeguards the heart from serious myocardial damage, the occurrence of a sudden occlusion may result in acute myocardial infarction if time is insufficient for the further development of adequate anastomotic vessels. Case 2 illustrates the presence of old occlusions of the coronary arteries and anastomotic circulation without symptoms of coronary insufficiency.

CASE 2.—No angina pectoris or congestive failure. Death due to biliary obstruction (fig. 2).

Carcinoma of pancreas and stone in ampulla of Vater. Complete occlusions of main stem and primary branch of left circumflex artery. Vessels distal to occlusions injected by collateral circulation from right coronary artery. Myocardium showed moderate fibrosis and no infarction (fig. 3).

This case illustrates that anastomotic circulation develops in relation to arterial occlusions. Despite the occlusions and narrowing of all three main arteries, no symptoms or signs of cardiac disease had been present.

6. Gross, Louis: The Blood Supply to the Heart in Its Anatomical and Clinical Aspects, New York, Paul B. Hoeber, 1921. Spalteholz, Karl Werner: Die Arterien der Herz wand, Leipzig, S. Hirzel, 1924. Campbell, J. S.: Stereoscopic Radiography of the Coronary System, Quart. J. Med. 22: 247, 1929.

The anastomotic circulation, so well visualized by the unilateral injection in this heart, must be considered largely responsible for the absence of cardiac pain or any area of infarction.

In the foregoing cases in which there was no fibrosis and no infarction, the coronary sclerosis leading to narrowing and occlusion evidently proceeded so slowly

TABLE 1.—*Angina Pectoris as Primary Cardiac Symptom; Thirty-Eight Cases*

	Cases
I. Complete old occlusion of one or more main coronary arteries.....	29 *
a. Without valvular lesions.....	24 cases
b. With valvular lesion.....	5 cases
II. Marked narrowing of one or more main coronary arteries.....	9
a. With valvular lesion of aortic stenosis.....	3 cases
b. With arterial hypertension.....	6 cases

\* Complete old occlusions of all three main coronary arteries were present in three cases, of two main coronary arteries in seventeen cases and of one coronary artery in nine cases.

TABLE 2.—*Cases of Congestive Failure with Angina Pectoris as Incidental Symptom; Nine Cases*

I. Combined coronary sclerosis and valvular lesions.....	2 cases *
II. Valvular lesions without coronary sclerosis.....	6 cases
III. Cor pulmonale without coronary sclerosis.....	1 case

\* Coronary sclerosis consisted of narrowing of one main coronary artery in one case and occlusion of one primary branch in the second case.

that the obstruction to blood flow could be compensated by the opening of collateral channels. Although serious damage is generally avoided by the development of such collateral circulation, the margin of safety or, as it may be termed, "coronary reserve" is presumably reduced. The caliber of the coronary pathways, while sufficient to supply the usual needs of the myocardium, may not be sufficient to meet extraordinary conditions imposed by fresh arterial occlusion, increased cardiac work or lowered blood pressure as in shock.

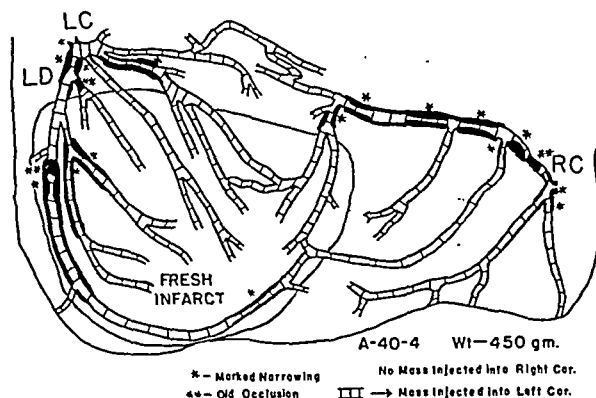


Fig. 4 (case 3).—Diagram of coronary arterial tree and site of myocardial infarct. Unilateral injection of lead agar mass into left coronary artery because of complete occlusion of right coronary artery.

To summarize, complete occlusion or narrowing of one or more major coronary arteries and their primary branches is found in the hearts of a considerable number of individuals without having given rise to cardiovascular signs or symptoms. Complete occlusion of one or more major coronary arteries is compatible with comfort and longevity. The function of the obstructed vessel is maintained satisfactorily by collateral pathways.

#### OBSERVATIONS IN CASES OF ANGINA PECTORIS

Following coronary occlusion the presence or absence of clinical signs and symptoms and the occurrence of myocardial damage depend on whether the development of the collateral circulation has kept pace with the progressive arterial narrowing. Our observations in cases of angina pectoris are in accord with the theory that cardiac pain develops when the coronary blood flow, while sufficient for the ordinary needs of the patient, is inadequate for the increased requirements of exercise, emotion and so on.

In the entire series of 355 cases there were forty-seven instances of angina pectoris (tables 1 and 2). In every case, examination of the clinical and pathologic data suggested the existence of relative insufficiency of the coronary circulation. This coronary insufficiency or reduced "coronary reserve" may be produced by factors which decrease the supply of blood or by factors which increase the myocardial requirements. The chief factor decreasing the blood supply is mechanical obstruction to blood flow by arteriosclerotic narrowing or occlusion. The collateral circulation enables the heart despite coronary obstructions to meet ordinary requirements but not the increased needs attendant to emotion or exertion. Among the chief factors which increase the work of the heart, and consequently increase its nutritional requirements, are valvular disease and arterial hypertension.

In accord with these considerations, we have divided all the patients in this series who experienced angina

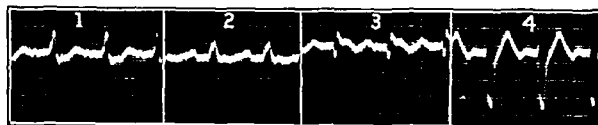


Fig. 5 (case 4).—Electrocardiogram taken four days before death.

pectoris into two groups. The first group of cases consists of those in which angina pectoris was the primary cardiac symptom (table 1). The second group comprises those patients in whom angina pectoris was present but was an incidental symptom, as the main cause of incapacity was congestive failure due, usually, to valvular heart disease (table 2).

*Cases in Which Angina Pectoris Was the Primary Cardiac Symptom* (table 1).—Old coronary arterial occlusions or narrowings of one or more of the main coronary arteries were found in each of the thirty-eight cases in which angina pectoris was the primary cardiac symptom. In the correlation of the coronary changes with the signs and symptoms of angina pectoris, fresh occlusions were not included in the foregoing analyses, for angina pectoris had been present prior to the occurrence of these terminal occlusions.

The numerous occlusions and narrowings observed in the hearts of this group are in striking contrast to the observations in the other hearts of the entire series. In each of these thirty-eight cases of angina pectoris the maximal blood supply originally available to the myocardium had been obviously reduced by arterial obstruction. Cardiac pain, presumably due to ischemia, developed under conditions which further reduced the available blood supply or increased the nutritional requirements of the heart. It is significant that, in the nine hearts in which coronary obstruction was somewhat

less extensive, other factors causing increased cardiac work were operative.

These anatomic observations provide an adequate structural basis for the operation of those physiologic factors which form the basis of the anoxic theory of angina pectoris.<sup>7</sup> In patients, previously well, who suddenly suffer attacks of mild or severe angina pectoris on but little exertion, the occurrence of progressive narrowing or complete occlusion of a coronary artery must be considered. A similar interpretation must be entertained in patients with long standing angina pectoris if attacks are suddenly more readily precipitated. Under such circumstances bed rest is strongly advisable to decrease the demands on the heart and to permit sufficient time for the development of more adequate collateral circulation.

*Cases in Which Angina Pectoris Was an Incidental Symptom in the Presence of Congestive Failure* (table 2).—In nine cases of the entire series of 355, angina pectoris was an incidental feature of the illness which was characterized mainly by the presence of congestive failure. Eight of these cases showed extreme degrees of valvular stenosis or insufficiency; the remain-

arterial occlusions are eliminated from the etiology of the angina pectoris. It is to be emphasized that, while there is a general relationship between the incidence of coronary occlusions and the occurrence of angina pectoris, other modifying factors such as the site of the occlusion, the importance of the vessel involved,<sup>8</sup> the adequacy of the collateral circulation, the rate at which such occlusions or narrowings develop and the influence of reflex and other physiologic changes such as spasm and the effects of emotion are also of great importance.

To summarize, every patient suffering primarily from angina pectoris without evidence of valvular disease or arterial hypertension has shown old complete occlusion of at least one major coronary artery at postmortem examination; in the majority of instances, old complete occlusions of at least two of the three main coronary arteries were found.

#### THE CLINICAL DIAGNOSIS OF CORONARY FAILURE

In certain cases of this series, cardiac pain more prolonged than that consistent with angina pectoris has been noted, but the clinical evidences of myocardial necrosis, such as fever, leukocytosis, increased sedimentation rate or progressive electrocardiographic changes over a period of days, were not observed. At postmortem the hearts did not show acute myocardial infarction. In accord with the concept that cardiac pain is due to relative myocardial ischemia, such attacks occasionally were coincident with increased demands on the heart, such as paroxysmal heart action, emotion or exertion, whereas in other instances decreased coronary blood flow following fall of blood pressure in shock was apparently responsible. Since these episodes are more prolonged than those of angina pectoris and, on the other hand, the signs of myocardial necrosis are absent, the clinical diagnosis of either angina pectoris or of acute myocardial infarction would be erroneous. These attacks are more accurately described as attacks of "coronary failure." If the "coronary failure" occurs under circumstances which have not previously provoked attacks, the clinical diagnosis of "coronary failure due to acute coronary occlusion" is justifiable. The exact pathologic mechanism of occlusion, i. e. atherosclerosis, thrombosis, ulceration of atheromatous plaques, subintimal hemorrhage or edema, and embolism, is beyond determination by clinical means. Since some cases of coronary failure are followed, after an interval of some hours or days, by an attack of acute myocardial infarction, such patients should be treated conservatively by bed rest for a week or more. This possible sequence of clinical events is the same as that described by Feil<sup>9</sup> and designated by him as "preliminary pain." Similarly, Sampson and Eliaser,<sup>10</sup> on the basis of observations on a series of cases, state that "A single spontaneous attack of prolonged anginal pain strongly suggests the approach of a typical coronary thrombosis."

To summarize, these episodes of "coronary failure" differ from angina pectoris in the longer duration of the attack and in some instances in the altered characteristics of the pain. Both coronary failure and angina pectoris have the same physiologic basis in reversible myocardial ischemia of shorter or longer duration. The terms "coronary occlusion" or "coronary thrombosis,"

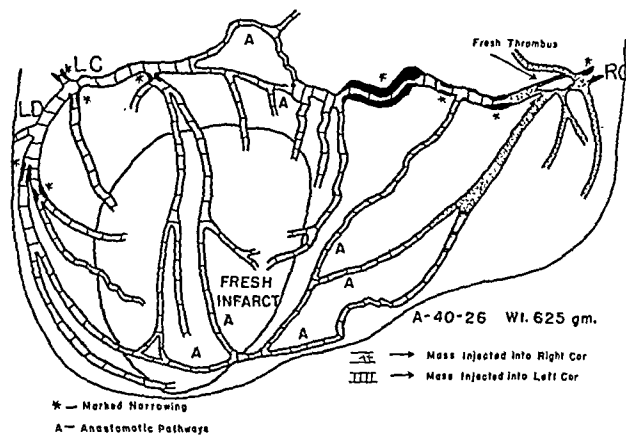


Fig. 6 (case 4).—Diagram of coronary arterial tree and sites of acute myocardial infarction and fresh thrombus.

ing case was one of cor pulmonale. In two of the cases of this group, arterial narrowings or occlusions also were found which undoubtedly tended to lower the capacity of the heart to accomplish the necessarily increased work.

*The General Relation Between the Incidence of Coronary Occlusions and Angina Pectoris* (table 3).—The incidence of occlusions has been examined in the following four groups of cases: (1) cases without angina pectoris, (2) cases with angina pectoris in which valvular disease was present, (3) cases with angina pectoris and associated arterial hypertension and (4) angina pectoris without valvular disease or hypertension (table 3). All hearts in which complete occlusion of any coronary artery was found are included in this table; eighty-six hearts conformed to this criterion. In these four groups the incidence of occlusions per heart rises progressively as factors other than

7. Parry, C. H.: An Inquiry into the Symptoms and Causes of the Syncope Anginosa, Commonly Called Angina Pectoris, Bath, R. Cruttwell, 1799. Keefer, C. S., and Resnik, W. H.: Angina Pectoris: A Syndrome Caused by Anoxemia of the Myocardium, Arch. Int. Med. 41:769 (June) 1928. Rothschild, M. A., and Kissin, Milton: Production of the Anginal Syndrome by Induced General Anoxemia, Am. Heart J. 8:729 (Aug.) 1933. Riseman, J. E. F., and Brown, M. G.: The Effect of Oxygen on the Exercise Tolerance of Patients with Angina Pectoris, Am. Heart J. 18:150 (Aug.) 1939. Smith, F. M.; Rathe, H. W., and Paul, W. D.: Observations on the Clinical Course of Coronary Artery Disease, J. A. M. A. 105:2 (July 6) 1935.

8. Schlesinger, M. J.: Relation of Anatomic Pattern to Pathologic Conditions of Coronary Arteries, Arch. Path. 30:403 (July) 1940.

9. Feil, Harold: Preliminary Pain in Coronary Thrombosis, Am. J. M. Sc. 193:42 (Jan.) 1937.

10. Sampson, J. J., and Eliaser, M., Jr.: The Diagnosis of Impending Acute Coronary Artery Occlusion, Am. Heart J. 13:675 (June) 1937.



as they are usually employed clinically, actually refer to an entirely different pathologic event; namely, myocardial infarction.

#### THE DIAGNOSIS OF MYOCARDIAL INFARCTION

If "coronary failure" is sufficiently prolonged, myocardial infarction results. The clinical diagnosis of acute myocardial infarction is based on the existence of prolonged cardiac pain plus clinical evidences of myocardial necrosis. These consist of fever, leukocytosis, increased sedimentation rate and electrocardiographic changes progressing over a period of days. Acute myocardial infarction may occur without a concomitant fresh thrombosis; and, contrariwise, thrombosis of a major coronary artery may occur without causing acute myocardial infarction.<sup>11</sup> Case 3 is an example of an acute myocardial infarction in the absence of fresh coronary occlusion:

CASE 3.—*Angina pectoris for two years; terminal syndrome of "acute myocardial infarction."*

*Complete old occlusions of main left anterior descending and right coronary arteries and primary branch of left anterior descending artery; multiple narrowings of coronary arteries; no recent occlusions; no old infarction; massive fresh infarction of left ventricle.*

Necropsy revealed the condition of the coronary arteries to be as shown in figure 4.

TABLE 3.—*Relation Between Incidence of Occlusions and Angina Pectoris*

Hearts with Occlusions	Number of Cases	Total Number of Occlusions	Aver. Number of Occlusions per Heart
Occlusions but no angina pectoris....	49	68	1.4
Angina pectoris with occlusions and valvular lesions .....	5	9	1.8
Angina pectoris with occlusions and arterial hypertension .....	19	39	2.1
Angina pectoris with occlusions only..	13	45	3.5

In the remaining 269 cases without occlusions, angina pectoris was absent except in nine with valvular defects and one with cor pulmonale.

The myocardium showed marked scattered fibrosis but no area of healed infarction. There was fresh infarction of the entire left ventricle and septum.

This case illustrates the following phenomena:

1. The high incidence of complete old occlusions of the main coronary arteries in cases of uncomplicated angina pectoris.
2. The amazing effectiveness of the collateral circulation in compensating for obstruction to the coronary blood flow so that no old infarcts had been produced in this heart.
3. The occurrence of fresh infarction in the absence of fresh occlusions.

The collateral circulation compensated to remarkable degree for numerous narrowings and occlusions throughout the coronary tree. As in most hearts of patients in whom angina pectoris was the primary cardiac symptom, two main coronary arteries were occluded. In addition, the primary branch of the left anterior descending artery was occluded and there were multiple areas of narrowing of all the arteries including the primary branches.

The effectiveness of this collateral circulation in preventing severe cardiac damage is evidenced by the

absence of any old infarction. It is also noteworthy that, prior to the terminal illness, the heart was able to meet the ordinary requirements of life, although the coronary reserve was limited. No signs of congestive failure had been present. As pointed out in a previous communication,<sup>2</sup> the temporary periods of ischemia and angina pectoris not infrequently leave fibrous scars and finally lead to congestive failure. The terminal episode of acute myocardial infarction was induced not by any fresh occlusion but by the increased demands of exercise

TABLE 4.—*Relation Between Acute Myocardial Infarction and Coronary Occlusions*

Number of Cases	Acute Myocardial Infarction at Necropsy	Fresh Coronary Occlusion
33.....	+	+
12 *.....	+	0

\* All hearts showed old complete occlusions except one with only slight narrowing in a case of cerebral hemorrhage with prolonged shock and respiratory paralysis.

during cold weather. Irreversible structural changes occurred leading to infarction of practically the entire left ventricle.

The clinical diagnosis of myocardial infarction caused by acute coronary occlusion would appear to be justified, however, when the sudden severe crushing pain and collapse with evidence of tissue necrosis occur under circumstances in which the work of the heart is not increased, i. e. during sleep or at rest or under conditions, such as walking, which impose no greater burden on the heart than the patient has regularly borne satisfactorily in the past.

In some instances of acute myocardial infarction caused by acute coronary occlusion the occlusion may be found distant from the infarct in a vessel serving as a source for the collateral circulation supplying that area. We have not uncommonly observed for example that, following the evidently gradual formation of an old complete occlusion of the left anterior descending artery, no myocardial infarct resulted. Subsequently, however, infarction of the anterior wall of the left ventricle was precipitated by a fresh occlusion in the right coronary artery which served as a source of collateral circulation to the left ventricle.

TABLE 5.—*Relation Between Old Occlusions and Myocardial Infarction \**

Number of Hearts with Old Occlusions	Old Myocardial Infarction	Acute Myocardial Infarction
15	+	0
11	0	+
26	0	0

\* Hearts with additional fresh obstruction to coronary arteries are excluded from this table.

This seemingly paradoxical sequence of events may be termed "infarction at a distance" and has been noted by others.<sup>12</sup> An excellent example of this phenomenon is case 4:

CASE 4.—*Angina pectoris and arterial hypertension three months before death; substernal thyroid with hyperthyroidism and congestive failure three weeks before death; terminal episode of acute myocardial infarction (fig. 5).*

11. Saphir, Otto; Priest, W. S.; Hamburger, W. W., and Katz, L. N.: Coronary Arteriosclerosis, Coronary Thrombosis, and the Resulting Myocardial Changes: Evaluation of Their Respective Clinical Pictures Including Electrocardiographic Records, Based on Anatomical Findings, *Am. Heart J.* 10: 567 (June) 1935. Friedberg, C. K., and Horn, Henry: Acute Myocardial Infarction Not Due to Coronary Artery Occlusion, *J. A. M. A.* 112: 1675 (April 29) 1939. Wolferth, J. B. 12. Bean, W. B.: Infarction of the Heart: A Morphological and Clinical Appraisal of Three Hundred Cases, *Am. Heart J.* 14: 684, 1937. Saphir, Priest, Hamburger and Katz.<sup>11</sup>



*Fresh occluding thrombus near mouth of right coronary artery; multiple narrowings of coronary arteries; extensive collateral anastomatic circulation; acute myocardial infarction of left ventricle (fig. 6).*

This case exemplifies:

1. The development of collateral arterial pathways in a heart with only narrowed arteries but no occlusions.
2. An instance of angina pectoris in which coronary insufficiency was produced by the increased demands on the heart due to arterial hypertension and hyperthyroidism in the presence of arterial narrowing.
3. Infarction at a distance.

Correlation of the electrocardiographic changes with the pathologic condition, while available only in a portion of the cases, is in accord with the observations of others in certain respects. Progressive electrocardiographic changes occurring over a period of days signify myocardial infarction. The pattern of the electrocardiographic changes conforms generally to the site of the infarction in the anterior or posterior portions of the left ventricle and bears no necessary relation whatever to the site of the coronary occlusion or indeed to the occurrence of a coronary occlusion.

#### THE CLINICAL USE OF THE TERMS "CORONARY THROMBOSIS" AND "CORONARY OCCLUSION"

The results of these studies indicate that the disparity between clinical diagnosis and the pathologic condition in the heart is largely due to the fact that the terms coronary thrombosis and coronary occlusion actually refer to a pathologic event which may give rise to various clinical syndromes or, indeed, to no clinical symptoms or signs. The present studies indicate that there is no characteristic syndrome necessarily associated with coronary arterial occlusion per se. In the past the terms "coronary thrombosis" and "coronary occlusion" have been used by many clinicians to denote acute myocardial infarction. Our observations as well as those by others<sup>13</sup> demonstrate, however, that acute myocardial infarction bears no necessary relation to the formation of thrombi or occlusions; either may occur in the absence of the other. In our series, twelve of forty-five hearts with acute myocardial infarction showed neither acute coronary thrombosis nor acute coronary occlusion (table 4). The use of the term "acute coronary occlusion" to designate the existence of acute myocardial infarction would have been inaccurate in these twelve, or 27 per cent of the cases of infarction; the term "acute coronary thrombosis" would have been inaccurate in 47 per cent. Conversely, twenty-six hearts showed old complete occlusion without any myocardial infarction (table 5). Eleven additional hearts had old occlusions and fresh myocardial infarction but no fresh occlusions; here again the terms "acute coronary thrombosis or occlusion" would have been incorrect.

The use of the terms angina pectoris, coronary failure or acute myocardial infarction to differentiate the various syndromes in which attacks of cardiac pain are witnessed is a modification of the terminology hitherto employed and conforms more accurately to the observed conditions found. Our data are in accord with the current belief that cardiac pain is a manifestation of myocardial ischemia. In all three of the aforementioned syndromes, i. e. angina pectoris, coronary failure and

acute myocardial infarction, the underlying mechanism seems to be a relative disproportion between the demands of the heart for blood and the supply of blood through the coronary arteries. The changes in the myocardium resulting from this disproportion depend solely on the extent and duration of the relative ischemia, not on the manner by which they are produced. If the duration of ischemia, as in angina pectoris, is brief, no permanent myocardial damage may occur or only microscopic foci of necrosis and fibrosis may result.<sup>14</sup> Even with more prolonged attacks, as in coronary failure, if the demands on the myocardium are quickly reduced by rest and sedatives or the control of abnormal cardiac rhythm, no structural damage may result. Clinical as well as experimental evidence<sup>15</sup> is in accord with these considerations. In the instance of myocardial infarction the ischemia is of such prolonged duration that irreversible structural damage results, giving rise to the clinical signs of tissue destruction.

#### SUMMARY AND CONCLUSIONS

1. A detailed clinical and pathologic study of 355 consecutive cases examined post mortem has been made with particular reference to the role of coronary occlusions and the collateral circulation in angina pectoris, coronary failure and acute myocardial infarction.

2. In normal hearts intercoronary anastomoses larger than 40 microns are generally absent. Fine communications measuring less than 40 microns in diameter can be demonstrated by the injection of watery solutions but are probably of little functional significance in obviating the untoward effects of sudden coronary narrowing or occlusion.

3. Complete occlusion or considerable narrowing of one or more coronary arteries may exist without giving rise to any clinical signs or symptoms and without having produced myocardial damage.

4. The apparent inconsistency between the presence of long standing obstructive arterial lesions and the absence of significant pathologic or clinical evidence of myocardial damage was dispelled by the demonstration of a collateral circulation which served as a bypass in relation to the obstruction in each of these hearts.

5. Every patient suffering primarily from angina pectoris without evidence of valvular disease or arterial hypertension has shown old complete occlusion of at least one major coronary artery at postmortem examination; in the majority of instances at least two of the three main coronary arteries had been occluded before the terminal illness.

6. Attacks of cardiac pain more prolonged than those of angina pectoris but unattended by evidence of myocardial infarction are more accurately described as attacks of coronary failure.

7. A comparative study of the clinical characteristics of coronary thrombosis and those of myocardial infarction forces the conclusion that coronary thrombosis and occlusion, per se, do not necessarily produce any characteristic clinical manifestations. The syndrome usually called "coronary occlusion," which consists of prolonged substernal oppression or pain, a fall in blood

14. Riseman, J. E. F., and Brown, M. G.: The Sedimentation Rate in Angina Pectoris and Coronary Thrombosis, *Am. J. M. Sc.* **194**: 392 (Oct.) 1937.

15. Blumgart, H. L.: Hoff, Hebbel E.; Landowne, Milton, and Schlesinger, M. J.: Experimental Studies on the Effect of Temporary Occlusion of Coronary Arteries in Producing Persistent Electrocardiographic Changes, *Am. J. M. Sc.* **194**: 493 (Oct.) 1937; Experimental Studies on the Effect of Temporary Occlusion of Coronary Arteries, *Tr. A. Am. Physicians* **52**: 210, 1937. Tennant, Robert, and Wiggers, C. J.: The Effect of Coronary Occlusion of Myocardial Contraction, *Am. J. Physiol.* **112**: 351 (June) 1935.

13. Wolferth, C. C.: Present Concepts of Acute Coronary Occlusion, *J. A. M. A.* **109**: 1769 (Nov. 27) 1937. Saphir, Priest, Hamburger and Katz.<sup>12</sup> Bean.<sup>12</sup>

pressure, pallor and the other manifestations of shock, and is accompanied by electrocardiographic changes, fever, leukocytosis and an increased sedimentation rate, in reality signifies myocardial infarction and should be so termed.

8. In all three of the discussed syndromes, i. e. angina pectoris, coronary failure and acute myocardial infarction, the underlying mechanism seems to be a relative disproportion between the requirements of the heart for blood and the supply through the coronary arteries. The changes in the myocardium resulting from this disproportion depend solely on the extent and duration of the relative ischemia, not on the manner in which they are produced.

9. The absolute necessity for immediate and complete bed rest, sedation, reduction of excessively high cardiac rates and other measures designed to reduce the work of the heart in the presence of prolonged cardiac pain is emphasized as a means of limiting the extent of myocardial necrosis or even preventing its development. Such a regimen also affords an opportunity for the development of a more adequate collateral circulation.

330 Brookline Avenue.

#### ABSTRACT OF DISCUSSION

DR. FRED M. SMITH, Iowa City: It has long been known that extensive collateral circulation may be present in the heart, particularly in the presence of arteriosclerosis of the coronary artery. Thus, effective communications may develop between two vessels when one is gradually obstructed. The work of Drs. Blumgart and Schlesinger and their co-workers emphasizes this feature and they are to be congratulated on the careful manner in which they investigated the problem. The development of collateral circulation is obviously a protective mechanism against the inroads on the circulation to the myocardium from the arteriosclerotic process. This accounts for the fact that the heart may be free from significant histologic changes even in the presence of the occlusion of one or more of the major coronary vessels. It may also explain the absence of symptoms or perhaps determine the character of the clinical manifestations. The function of the collateral circulation gives us an important insight into the treatment of the condition. If a means can be found by which the development of this feature can be promoted it will obviously represent a tremendous advance in the treatment.

DR. WILLIAM D. STROUD, Philadelphia: We have been talking for a long time about collateral circulation, but it has remained for Dr. Blumgart and his associates to demonstrate to us definitely that this process does develop in the heart. I think it should be a great comfort to know that the process of collateral circulation develops, since most of us, as physicians, are going to develop angina with coronary disease. Although this development of the collateral circulation goes on, we may be able to help it with xanthines. It is encouraging to know that this process does go on, and it should stimulate us to be encouraging to our patients. With every one reading newspapers nowadays and seeing that many people die with this condition, it is discouraging and, as physicians, we possibly tend to increase this discouragement by our apprehension.

DR. HERRMAN L. BLUMGART, Boston: The most striking finding in this work by the method of Dr. Schlesinger has been the high incidence of coronary occlusions. The abrupt onset of angina pectoris in a person previously well, the sudden onset of angina pectoris on but slight exertion, or a marked exacerbation in the intensity or frequency of attacks of angina pectoris is presumptive evidence of coronary occlusion or progressive narrowing, which has exceeded the rate of development of the collateral circulation. Such patients should be treated conservatively by bed rest or by reduction of effort, so that their lives will not be unnecessarily jeopardized and the more serious consequences of myocardial infarction may possibly be avoided.

## CLINICAL EVALUATION OF DISABILITY IN PULMONARY DISEASES OF INDUSTRY

EDGAR MAYER, M.D.

NEW YORK

The New York State Department of Labor has created a board of impartial consultants to review controversial claims for compensation due to pulmonary disability acquired in industry. As a member of this board it has been my experience that two major problems exist:

1. A patient presents pulmonary disease obviously related to a definite industrial hazard. Disability is claimed, and it must be decided whether the disease which is present is disabling.

2. A patient is obviously disabled, but the difficulty arises in determining whether his disability is related to his occupation.

The solution of these problems necessitates finding answers to the following questions:

1. What etiologic agents exist in industry which produce pulmonary damage?

2. How do these substances produce lung injury, and what are the anatomic results?

3. How can these pulmonary illnesses be recognized?

4. How do these illnesses produce pulmonary incapacity, and what reliable clinical and laboratory procedures are there for determining this disability?

#### ETIOLOGY

Pulmonary diseases of industry include all forms of pulmonary fibrosis and emphysema produced by exposure to dusts, fumes, vapors and gases. Besides the specific pneumoconioses such as silicosis and asbestosis, pulmonary fibrosis may be produced by a variety of other industrial hazards.

In the practical problem of compensation in industry the relationship of the pulmonary disease to a specific exposure may be reasonably established in two ways. Either the exposure directly produces the pulmonary fibrosis or it favors the development of chronic low grade inflammation which results in fibrosis. It is well established that the accumulation of even inert substances in the lung predisposes it to recurrent low grade infections.

Individual susceptibility is an important factor, as evidenced by the experience that under identical conditions of exposure the extent and character of the lesions vary from one person to another, as well as the disability associated with apparently similar lesions. The constitutional factor, age, previous infections and nonindustrial dust exposure are important in determining individual reactions.

*Constitutional Factor.*—This has an important but poorly understood role. Just as individual factors exist in resistance to infection, so individual constitutional variants in the capacity of the lung to deal with foreign matter influence the reaction to hazardous exposure. One can only speculate on these factors. Variable ciliary action and circulatory flow probably contribute to the reaction.

From the New York Hospital and the Department of Medicine, Cornell University Medical College.

Read before the Section on Preventive and Industrial Medicine and Public Health at the Ninety-First Annual Session of the American Medical Association, New York, June 12, 1940.

*Age Factor.*—Pulmonary efficiency diminishes with age; the diminution of it becomes manifest as emphysema. In some this comes only in senility, but, as with other degenerative processes, it may develop much earlier. Inelastic lungs are more susceptible to injury by foreign substances. In addition to the loss of elasticity with increasing age, there is a greater or lesser degree of associated fibrosis. This represents, no doubt, the cumulative effect of the two following elements:

1. Few people pass through life without repetitions of minor pulmonary incidents called colds, grip, influenza or bronchitis.

2. Furthermore, particularly in cities and industrial centers, constant inhalation in the general atmosphere of particulate matter, vapors and fumes of every description takes place.

These respiratory infections and this general dust exposure eventually provoke pulmonary changes. There exist only differences in degree, not in kind, between the so-called normal amount of pulmonary fibrosis so prevalent in the general population and those severe fibrotic processes which destroy the lungs of workers in industries wherein exposures exist to more concentrated and continuous effect of the same agents present in greater dilution in the atmosphere of industrial centers.

#### PATHOGENESIS

Prolonged exposure to pulmonary hazards produces morphologic changes in the lung which are an expression of the failure of the self-cleansing function of this organ. This function may be defined as the process by which foreign particulate substances and the products of inflammation (fluid as well as cellular) are eliminated from the air spaces. The active factors in this process are particular cells (alveolar phagocytes), lymphatic and blood circulations of the lungs and the ciliary apparatus of the air passages. This self-cleansing action is normally so efficient that it can clear, within a few hours, the air spaces of such huge exudates as may occur in lobar pneumonias. Its failure under conditions of industrial exposure results in accumulation of foreign matter in the air spaces. This provokes a chronic productive inflammation known as pulmonary fibrosis. There results a reduction in the available breathing space and in pulmonary elasticity. Progressive pulmonary emphysema is invariably associated with the development of the fibrosis. At first this emphysema is of compensatory character, but eventually it must become a source of decompensation, as overdilatation of the already inelastic lung becomes irreversible.

A discussion of the morphology of fibrosis and emphysema is outside the scope of this presentation, but explanation of the following morphologic divisions will aid in understanding practical questions to be discussed later.

From the clinical and roentgenologic points of view, pulmonary fibrosis may be classified in the following forms: (1) massive (pneumonic subacute; this is seen in acute silicosis and after radium and roentgen ray exposures. Pathologically there is organized pneumonic exudate with recent cellular infiltration of monocytes and fibroblasts, (2) diffuse interstitial, (3) whorled nodular and (4) conglomerate (silicosis with infection and anthracosilicosis).

Diffuse interstitial fibrosis is seen in early silicosis. Both diffuse and nodular whorled fibrosis may terminate in the conglomerate type which has resulted in infection.

Emphysema associated with the various fibroses differs greatly both in degree and in nature. Fibrosis

and emphysema rival each other, producing predominating structural changes. At times fibrosis predominates and at others emphysema is the conspicuous factor. Conglomerate fibrosis is more likely to give extensive emphysema. Bullae frequently are found bordering on fibrotic plaques. The massive pneumonic type of fibrosis is too rapid in evolution and too extensive to develop emphysema. Interstitial and nodular forms more likely produce diffuse generalized and compensatory emphysemas.

The first problem is estimation of disability in a patient with obvious pulmonary fibrosis related to his industry.

#### REPORT OF CASES

CASE 1.—E. B., aged 52, had been a construction and tunnel worker for eighteen years, he had been singularly free from illness, stating specifically that he never got colds and had not been laid up in bed since childhood. He complained of shortness of breath on climbing stairs or walking moderate distances such as five blocks. In addition he had a hacking cough which was productive of 10 cc. of mucoid sputum daily. Furthermore, he stated that he was not strong enough to handle a pneumatic drill and that this work provoked cough and shortness of breath. He claimed disability. What objective criteria can be used to establish this man's claim?

Physical examination disclosed a muscular, well nourished man whose accessory muscles were being used at a slightly increased rate of respiration. His chest was not barrel shaped, but there was definite limitation of thoracic cage motion. There was no cyanosis. The cardiac impulse was not palpable, and the heart sounds were distant, with an accentuated pulmonic second sound. The chest showed normal resonance above, hyperresonance below; fluoroscopic examination showed diminished diaphragmatic movement; there was no difference between inspiration and expiration. A roentgenogram showed emphysema below and a markedly increased retrocardiac space. The breath sounds were reduced in intensity but were vesicular in nature, and forced breathing failed to increase their intensity as it normally should. No rales were heard. A roentgenogram showed conglomeration and mottling. In this patient, who did not show extreme disability, there was, nevertheless, definite evidence on physical examination alone of reduced pulmonary capacity sufficient to explain his disability. This was a simple, clearcut case.

CASE 2.—Another man with a similar history of exposure, in whose roentgenograms conglomeration and mottling shadows but no obvious emphysema appeared, claimed disability because of shortness of breath and cough. Physical examination failed to show any definite evidence of pulmonary disability. His breathing was little changed and his chest excursion practically normal, as were his breath sounds and cardiac action. Fluoroscopic examination revealed good motion of the diaphragm, which was smooth in contour. There was no increase in the retrocardiac space, and the lungs did not appear overilluminated.

As neither physical examination nor fluoroscopic and roentgen ray studies were conclusive for determining disability in this patient, I had to use functional tests as accessory procedures.

Pulmonary function may be disturbed in three ways: (a) in ventilation, (b) in gas exchange and (c) in pulmonary circulation.

1. By ventilation is meant the ability of the lung to inflate and deflate with air. An increase of the residual and the tidal air takes place at the cost of the reserve air, leading thus to a progressive increase of the permanent air content of the lungs characteristic of pulmonary fibrosis associated with emphysema. This obviously interferes with the capacity of the lung to inflate and deflate. There results an increase in the minute volume of ventilation, while at the same time the maximal breathing capacity is reduced. Maximal breathing capacity is the total volume of air that can

be turned over during a minute's time by the deepest and most rapid respiration. It is calculated from the vital capacity and multiplied by the highest rate per minute the patient can actually accomplish.

2. With gas exchange tests one can measure spirometrically respectively the oxygen intake and carbon dioxide output. This is expressed in essentially three ways:

(a) Oxygen debt is the amount of excess oxygen the normal person needs at the end of exertion. It usually takes one to two minutes to recover the oxygen necessary to relieve dyspnea. Decompensation of the gas exchange mechanism is evident when the recovery period is longer than three minutes.

(b) Oxygen deficit is revealed by the excess intake of oxygen utilized when a patient shifts from air to oxygen inhalation. This is a sign of latent oxygen want which may be present at rest. It is found, despite full oxygen saturation of the blood, in pulmonary diseases bordering on decompensation.

(c) Oxygen unsaturation of the hemoglobin of the arterial blood, as determined by gas analysis, is found in disturbed gaseous exchange. Normally the oxygen saturation of arterial blood is about 95 per cent; saturation below 93 per cent indicates anoxemia, a sign of deficient oxygen supply. With a normal quantity of hemoglobin, this anoxemia indicates either interference with diffusion of gas in the lungs, poor ventilation or failing circulation. Artificially produced oxygen unsaturation is used as a test of functional deficiency (Whitehead et al.) by having the patient breathe a low oxygen mixture.

3. A third test of pulmonary function is that of measuring the efficiency of the pulmonary circulation. The simpler forms of such tests are determinations of the circulation time from arm to lung, and from arm to tongue and to carotid sinus by use of ether, dehydrochloric acid, sodium cyanide or calcium. This determines delay in circulation through the lungs. Intravenous infusion of 1,000 cc. of fluid followed by study of its effect on venous pressure and vital capacity reveals loss in reserve of the pulmonary vascular bed by the proportionate rise in venous pressure and decrease of vital capacity respectively.

The foregoing three functions, ventilation, gas exchange and pulmonary circulation, may be tested in combination under conditions of graded exercise. It has been found that for practical purposes the most suitable procedure is the so-called exercise tolerance test. The standard of exercise employed in this test is 30 steps per minute on a 20 cm. high pedestal. The patient exercises while connected with a spirometer which enables the examiner to measure the volume of air displayed per minute before, during and after exercise. The main purpose is to estimate the exercise capacity of the patient by this standard test, which is to find the point of exertion at which the patient registers inability to continue because of dyspnea.

The actual ventilatory volume measured at the dyspnea point, when related to the maximum breathing capacity of the patient (as calculated from vital capacity and maximal rate of breathing), affords information as to whether or not the patient is functionally handicapped.

A patient dyspneic on the aforementioned standard exercise, for which he needs 60 per cent or more of his maximal breathing capacity, is recognized as func-

tionally handicapped. The amount of reserve remaining available in this standard exercise may be considered a crude measure of the patient's exercise capacity (where the reserve expresses the difference between maximal breathing capacity and actual minute volume of ventilation).

The normal person is comfortable with exercise requiring only 25 per cent of the maximal breathing capacity, uncomfortable on using 50 per cent and dyspneic on using above 60 per cent of maximal breathing capacity.

The exercise tolerance test is, then, essentially a measure of dyspnea. Clinically, dyspnea should be spoken of only when it is elicited by exertion employed in one's ordinary daily activities, such as moderate exercise. Under such conditions dyspnea indicates that the functional facilities no longer meet the ordinary demands without the patient's conscious effort at increased function. It should not be confused with hyperpnea, which is normally present on severe exertion.

Recent studies indicate that the nervous regulation of breathing is evidently much more sensitive than is the chemical. Most workers believe that the dyspnea of pulmonary disease is usually reflex in origin and in the forms of greatest clinical importance is associated with pulmonary congestion. Dyspnea might best be explained as a distress signal for the approaching limit of efficiency in coordination of ventilation, gas exchange and circulation. In this sense the point of dyspnea in exercise, when accurately determined, is perhaps the truest measure of a person's functional capacity.

In final analysis, then, evaluation of disability must be made by employing all available clinical data in conjunction with the simpler test of functional capacity. A single measuring stick, unfortunately, does not exist in the present state of our knowledge. When clinical data are inconclusive, the exercise tolerance test, as described previously, will at times give sufficient evidence of disability. At other times discrepancies exist, and opinion can be rendered only on the basis of one's clinical judgment.

#### DISABILITY GRADING

Disability should be graded according to the levels of functional compensation and decompensation, as explained. In conclusion the following classification, with its implications, is submitted for consideration as applying specifically to pulmonary diseases of industry:

*Phase of Compensation.*—Pulmonary fibrosis and emphysema are present to a considerable degree. They are apparent in visible distention of the lungs and demonstrable by roentgen examination, physical signs and spirometric tests. These indicate the presence of definite emphysema which, however, is still compensatory in character and does not as yet restrict functional capacity for moderate exercise. The vital capacity is reduced to more or less marked degree.

*Latent Decompensation.*—Fibrosis and emphysema apparent by all tests are of an extensive degree and, while tolerated during rest without producing symptoms, are associated with marked restriction of exercise capacity. Dyspnea is readily elicited on moderate exercise.

*Manifest Decompensation.*—Here the fibrosis and emphysema are of such degree as to be associated with more or less constant symptoms of functional insufficiency (dyspnea) even while the patient is at rest.

470 Park Avenue.

## ABSTRACT OF DISCUSSION

DR. J. BURNS AMBERSON JR., New York: The point in Dr. Mayer's discussion which I should emphasize is his last statement that the estimation of a patient's disability after thorough study becomes largely a matter of clinical judgment. Physical and roentgen examination, of course, may disclose the extent and nature of the lesions, but impairment of function may be relatively slight even though the lungs are widely involved. What I refer to particularly is the distinction between nodular fibrosis of the lung such as one sees in silicosis, in which the functional disability may be relatively slight, and strictly interstitial fibrosis, which may be demonstrated with difficulty in the roentgenogram but, possibly because of the compromise of the capillary bed, may give rise to severe respiratory disability. The constitutional and physiologic factors which enter into disability after exposure to dust, for instance, are important; among these are to be considered the efficiency of the filtering mechanism of the nose and the disposition to such complications as sinusitis. There is some evidence that miners who suffer from sinusitis or come from families in which there is prevalence of respiratory infections seem to develop disability sooner than others. Estimation of respiratory dysfunction, as Dr. Mayer has indicated, is rather complicated and elaborate and certainly has to be subjected to clinical interpretation. Consideration should be given the man's estimate of what he can tolerate under working conditions. One has to think not only of mechanical functional disability but also of the possible threat of infection, present or future. As Dr. Mayer emphasized, a patient with pulmonary fibrosis and emphysema tolerates any pulmonary infection less well than the patient with normal lungs. This is particularly striking in the case of bronchopneumonia, in which relatively slight involvement causes often serious pulmonary decompensation. The threat or the actual effect of tuberculosis is always important to determine.

DR. EDGAR MAYER, New York: The aim of our studies now is to compare the value of clinical criteria of functional disability, as determined by physical signs, roentgen and fluoroscopic findings with that of the simpler functional tests. We are also aiming to compare on large enough scale Peabody's formula for predicting the value of maximal effective volume of breathing with the exercise tolerance and maximum breathing capacity test.

ADRENAL CORTEX EXTRACT IN THE  
TREATMENT OF BROMIDE ERUPTION  
AND BROMIDE INTOXICATION

C. P. BONDURANT, M.D.

AND

COYNE CAMPBELL, M.D.

OKLAHOMA CITY

Our purpose in this paper is to report the effect of adrenal cortex extract<sup>1</sup> on the elimination of bromide and bromide effects, with special reference to bromide eruption and bromide intoxication. This report is based on our experience and the evidence accumulated from the treatment of five cases of bromide eruption and nine cases of bromide intoxication. Also we give the results of the study of ten cases of bromism which we had the opportunity of observing in epileptic patients at the Central State Hospital.

A short review of the pharmacology of bromides reveals that Bolgar<sup>2</sup> in 1910 found that bromides were readily absorbed from mucous membranes and that in ligated intestinal segments the absorption of bromide was not delayed by the presence of chloride; but

bromide delayed chloride absorption. There are a variety of opinions present in the literature dealing with the distribution of bromide between the blood and various body fluids and tissues following its absorption. It has been reported that the distribution ratio between the bromides in the red blood cells and the serum is lower,<sup>3</sup> the same as<sup>4</sup> and higher<sup>5</sup> than the corresponding chloride ratio. Likewise, research opinions are at variance on the bromide-chloride content of various tissues. Two extensive and excellent independent studies, however, were carried out by Weir and Hastings<sup>6</sup> and by Wallace and Brodie<sup>7</sup> on the bromide-chloride distribution in various tissues; they agreed that, after oral and intravenous administration, the wet tissue serum ratios of bromide and chloride were in close agreement for all tissues except the brain and spinal fluid, and they further agreed that bromide has been found to replace chloride throughout the body tissues and fluids except for the brain and spinal fluid. In our work the blood bromide content has been taken as an index of progress in bromide elimination. As early as 1894 this replacement theory was suggested by Nencki and Schoumow-Simonowsky,<sup>8</sup> who found that those organs which normally contain the largest amounts of chloride also contain the largest amounts of bromide, and as the bromides increased the chlorides decreased. This work has been both confirmed and denied. Tachau<sup>9</sup> found that the bromide was excreted mainly in the urine; it has been claimed by Hastings, Harkins and Liu<sup>10</sup> and denied by von Frey<sup>11</sup> that the kidneys preferentially excrete chloride over bromide. Wyss<sup>12</sup> found that urinary excretion of bromide starts promptly after administration but proceeds slowly and that there is a disturbed ratio between the amount of bromide given and that excreted. Herzfeld-Gormidor<sup>13</sup> found bromide excreted in a ratio to the amount given, but always with retention, and noted traces of bromide in the urine as long as twenty days after administration was stopped. Wyss<sup>12</sup> and Herzfeld-Gormidor<sup>13</sup> were in accord in their conclusion that the administration of chloride hastened the elimination of bromide and, conversely, that the administration of bromide increased the elimination of chloride. In 1922, and more conclusively in 1923, Wile and his co-workers,<sup>14</sup> first suggested the chloride therapy of bromide eruption and laid the foundation for much future work.

Until recently Addison's disease, which basically is a degeneration of the adrenal glands, has been treated mainly by the oral and intravenous administration of large amounts of sodium chloride. More recently this chloride therapy has been fortified by the intramuscular injection of solutions of adrenal cortex; this addition to the older therapy has had exceptional success. The

3. Guillaumin, C. O., and Merejkowsky, B.: *Compt. rend. Soc. de biol.* **113**: 1428, 1933.

4. Palmer, J. W., and Clarke, H. T.: *J. Biol. Chem.* **99**: 435 (Jan.) 1933.

5. van Dyke, H. B., and Hastings, A. B.: *J. Biol. Chem.* **92**: 27 (June) 1931.

6. Weir, E. G., and Hastings, A. B.: *J. Biol. Chem.* **129**: 547 (Aug.) 1939.

7. Wallace, G. B., and Brodie, B. B.: *J. Pharmacol. & Exper. Therap.* **65**: 214 (Feb.) 1939.

8. Nencki, M., and Schoumow-Simonowsky, E. O.: *Arch. f. exper. Path. u. Pharmacol.* **34**: 313, 1894.

9. Tachau, H.: *Arch. f. exper. Path. u. Pharmacol.* **66**: 334, 1911.

10. Hastings, A. B.; Harkins, H. N., and Liu, S. K.: *J. Biol. Chem.* **94**: 681 (Jan.) 1932.

11. von Frey, E.: *Ztschr. f. exper. Path. u. Therap.* **8**: 29, 1910.

12. Wyss, V. H.: *Deutsche med. Wchnschr.* **39**: 345, 1913.

13. Herzfeld-Gormidor, C.: *Zentralbl. f. Biochem. u. Biophys.* **13**: 790, 1912.

14. Wile, U. J.; Wright, C. S., and Smith, N. R.: *A Preliminary Study of the Experimental Aspects of Iodid and Bromid Exanthems, Arch. Dermat. & Syph.* **6**: 529 (Nov.) 1922. Wile, U. J.: *Further Contributions to the Experimental Aspects of Iodid and Bromid Exanthems, ibid.* **8**: 407 (Sept.) 1923.

Read before the Section on Dermatology and Syphilology at the Ninety-First Annual Session of the American Medical Association, New York, June 14, 1940.

1. The adrenal cortex extract used was the Parke, Davis & Co. product Eschatin.

2. Bolgar, G.: *Arch. internat. de pharmacodyn. et de therap.* **19**: 311, 1910.

depleted chloride content of the system can be maintained at physiologic levels and the patients are seen to recover almost to a normal state. In the older literature considerable discussion was centered on the relation between the adrenals and the metabolism of sodium, potassium and chloride; more recently Loeb and his associates<sup>15</sup> and Harrop and his associates<sup>16</sup> agreed that a regulatory effect on sodium and chloride metabolism is one of the functions of the adrenal cortex. In the last three years a great deal of work has been done

adrenal cortex extract forces a definite retention of sodium chloride. Since it is apparent that bromide is retained in the system at the expense of chloride, adrenal cortex extract was given in the treatment of bromide retention in the cases reported here and the results are recorded.

The toxic level of serum bromide is a variable factor with reference to the individual case and until recently has not been well understood. An excellent study on this phase of bromide retention was published by

TABLE 1.—Cases of Bromide Intoxication

Case	Condition on Admission	Serum Bromide on Admission, Mg.	Sodium Chloride Given, Gm. Daily	Adrenal Cortex Extract Given	Subsequent Serum Bromide, Mg.	Days After Admission	Condition at That Time
1	Severe bromide intoxication.....	400	8-10	None	200	18	Still confused
2	Mild intoxication.....	150	6	5 cc. per day	50	2	Relieved of bromide intoxication
3	Severe bromide intoxication.....	360	6-10	5 cc. per day	115	4	Normal
4	Severe bromide psychosis.....	300	6-10	None	157	12	Still confused
		300	6-10	5 cc. per day	63	14	Practically normal
5	Severe bromide psychosis.....	350	8-10	5 cc. per day	80	4	Relieved of bromide intoxication; epilepsy
6	Moderate intoxication.....	200	6-10	5 cc. per day	60	2	Relieved of bromide intoxication; involutional psychosis
7	Severe intoxication with dementia paralytica	165	8-10	5 cc. per day	105	1	Relieved of bromide intoxication
8	Severe intoxication.....	250	8-10	5 cc. per day	100	4	Normal
9	Severe intoxication.....	300	8-10	5 cc. per day	75	5	Normal

TABLE 2.—Cases of Bromism in Epilepsy Artificially Produced

Case	4/1/40	4/4/40	4/9/40	4/16/40	4/20/40	4/21/40—4/22/40	4/23/40	4/24/40	4/26/40	4/27/40	5/1/40	5/4/40	5/7/40	5/10/40	Total Bromide, Grams
Treatment Given—Sodium Chloride and Adrenal Cortex Extract															
1 Chloride.....	501.6	481.4	426.0	338.0	247.0	232.2	212.6	237.4	264.2	291.2	302.0	332.4	401.8	463.4	502.2
Bromide.....	13.02	144.0	220.0	236.0	244.0	254.0	188.0	270.0	190.0	120.0	94.0	62.0	40.0	22.0	8.0 2,400
2 Chloride.....	693.2	660.3	620.4	421.0	242.6		158.0	204.1	312.5	321.0	360.0	424.8	439.1	463.6	482.1
Bromide.....	20.5	81.4	210.0	228.0	253.0		245.0	173.0	154.0	102.0	78.0	40.0	12.0	3.0	1.8 2,280
3 Chloride.....	198.4	190.7	185.0	139.3	102.1		207.1	236.0	266.7	268.1	267.0	279.3	301.8	332.3	401.0
Bromide.....	22.5	62.5	183.0	250.0	374.0		274.0	150.0	96.0	75.0	68.0	37.0	15.2	10.3	6.2 2,280
4 Chloride.....	202.9	184.7	183.4	132.0	121.6	103.4		97.0		88.3	117.6	221.4	315.0	337.6	
Bromide.....	12.0	37.0	74.0	83.0	104.0	170.0		198.0		257.0	164.0	55.0	40.5	27.0	2,340
Treatment Given—Chloride Alone															
5 Chloride.....	518.1	502.4	436.0	300.7	160.4		351.0	379.2	420.0	446.8	449.0	496.3	532.0	587.0	592.4
Bromide.....	18.02	54.0	127.0	216.0	327.0		272.0	268.0	204.0	162.0	160.0	150.0	145.0	130.0	120.0 2,280
6 Chloride.....	495.2	443.8	424.7	301.0	132.4		215.4	301.7	387.2	389.4	378.0	389.0	392.6	393.1	396.8
Bromide.....	24.40	96.7	250.0	286.7	296.0		278.0	275.0	252.0	246.0	220.0	196.0	174.0	145.0	140.0 2,280
7 Chloride.....	421.3	401.2	400.4	316.7	243.0	204.3		188.0		186.1	199.3	208.8	216.0	288.2	
Bromide.....	9.02	46.0	83.0	117.0	159.0	210.0		231.0		263.0	194.8	175.0	160.0	130.0	2,340

in this form of treatment of Addison's disease; Loeb,<sup>17</sup> Thorn,<sup>18</sup> Thompson,<sup>19</sup> Harrop,<sup>20</sup> Cutler<sup>21</sup> and Hartman<sup>22</sup> are in agreement that the administration of

Gundry<sup>23</sup> in which he presents detailed information on fifteen cases of bromide intoxication. In his article he gives a correlation between the level of the bromide content in the serum and mental symptoms. He indicated that, when the serum bromide reached from 150 to 250 mg. per hundred cubic centimeters of serum, mental symptoms appeared. In the management of his cases he used sodium chloride alone, from 4 to 10 Gm. daily for an average of two weeks, after which time the serum bromide level ranged from 85 to 244 mg. per hundred cubic centimeters and mental symptoms ranged accordingly.

15. Loeb, R. F.; Atchley, D. W.; Benedict, E. M., and Leland, J.: *J. Exper. Med.* 57:775 (May) 1933.

16. Harrop, G. A.; Softer, L. J.; Ellsworth, R., and Trescher, J. H.: *J. Exper. Med.* 58:17 (July) 1933.

17. Loeb, R. F.: Treatment of Addison's Disease, *J. A. M. A.* 112:2511 (June 17) 1939.

18. Thorn, G. W.; Howard, R. P., and Emerson, Kendall, Jr.: *J. Clin. Investigation* 18:449 (July) 1939.

19. Thompson, W. O.; Thompson, P. K.; Taylor, S. G., and Hoffman, W. S.: *Endocrinology* 24:774 (June) 1939.

20. Harrop, G. A.: *J. Exper. Med.* 57:305 (Feb.) 1933.

21. Cutler, H. H.; Power, M. H., and Wilder, R. M.: Concentration of Chloride, Sodium and Potassium in Urine and Blood: Their Diagnostic Significance in Adrenal Insufficiency, *J. A. M. A.* 111:117 (July 9) 1938.

22. Hartman, F. A.; Lewis, L. A., and Toby, C. G.: *Endocrinology* 22:207 (Feb.) 1938.

23. Gundry, L. P.: Bromide Intoxication, *J. A. M. A.* 113:466 (Aug. 5) 1939.



The nine cases of bromide intoxication which we report in table 1 were seen in the Campbell Clinic and are reported after hospital observation. In two of these cases treatment was by chloride alone and in seven adrenal cortex extract was given in conjunction with the chlorides. Dosage was the amount indicated in table 1. The two cases in which chloride was given alone make an interesting comparison to the other seven of this group. Their average duration of mental symptoms was more than fifteen days. The average of the other seven cases was five and one-half days.

The five cases involving the skin reported here are from our private files and from the University Hospital service.

#### REPORT OF CASES

**CASE 1.**—A white woman aged 39, seen first June 4, 1939, gave a history of prolonged nervousness and of having taken bromides intermittently over a period of years. Two months previous to the appearance of the lesions on her legs she had

activity typical of bromide eruption which were separated by scarring from previous lesions. The process had been present many months. Secondary infection was apparent. The blood bromide level was 223 mg. per hundred cubic centimeters. Other laboratory studies were negative. His treatment consisted of 8 Gm. of sodium chloride by mouth, sodium bicarbonate 1 drachm (4 Gm.) and adrenal cortex extract 5 cc. intramuscularly daily. This was continued for seven days. There were no other sedatives given and the child had one seizure during his hospital stay. The lesions were treated locally with wet packs. The healing process was apparent at the end of the first week and this had progressed almost to a smooth scarred but hyperemic area when he was discharged from the hospital at the end of the fourth week. The blood bromide level on discharge was 26 mg.

**CASE 4.**—A white man aged 37, a stock broker, had a papular eruption about his face, forehead and shoulders which had been present for three weeks. The lesions were brown, crusted and painful. He was nervous and addicted to drinking from two to five effervescent bromides daily. His blood bromide level was 62 mg. per hundred cubic centimeters of serum. He was given 5 Gm. of sodium chloride by mouth and 3 cc. of adrenal cortex extract intramuscularly daily for four days. His skin was healed at the end of the third week.

**CASE 5.**—A white woman aged 29 had consulted me five years previously to the present admission with a typical bromide eruption. She had changed her family doctor and had been given bromide for her persistent nervousness for six weeks prior to seeing me. Her dosage had been approximately from 60 to 75 grains (4 to 5 Gm.) daily. About a week and a half after this medication was started she received two scratches on her left lower leg. One scratch was about 3 inches long, and the other about  $\frac{3}{4}$  inch long. These scratches soon



Fig. 1 (case 5).—Bromide eruption in traumatized area on leg scratched by wire.

taken large doses of bromide constantly, approximately from 60 to 100 grains (4 to 6.5 Gm.) daily. The lesion first appeared on the posterior aspect of her lower leg as a small papule and gradually enlarged to form an irregular oval lesion 3 cm. in diameter. The surface was raised, papilliform and fungating, with many small abscesses visible. The surrounding skin was red, swollen and painful. The laboratory examinations were essentially negative except for the blood bromide level, which was 85 mg. per hundred cubic centimeters of serum. Treatment was the daily administration of 200 cc. of physiologic solution of sodium chloride intravenously and 3 Gm. of sodium chloride by mouth with the intramuscular injection of 2.5 cc. twice daily of adrenal cortex extract. This treatment was continued for six days. On the second day the bromide level of the blood was 66 mg., the third day 37 mg. and the sixth day 15 mg. per hundred cubic centimeters of serum. The lesions were more painful the second and third days and were treated locally by wet dressings. The healing was noticeable at the end of the first week and the lesion was entirely healed, to leave a hyperemic scar, at the end of the fifth week.

**CASE 2.**—A white woman aged 42, seen first Aug. 11, 1939, gave the usual history of bromide medication over a long period, most of this being in the form of "patent medicines." The eruption was primary on her leg and was typical of bromide eruption—painful, raised and with the usual cribriform surface. The surrounding skin was irritated by local medication. Her blood bromide level was 97 mg. per hundred cubic centimeters. She was given six days of treatment consisting of 5 cc. of adrenal cortex extract intramuscularly, 200 cc. of physiologic solution of sodium chloride intravenously and 5 Gm. of sodium chloride by mouth each day. On the third day her blood bromide level was 68 mg. and on the fifth day it was 20 mg. per hundred cubic centimeters of serum. Saline packs were applied locally. The lesion progressed to almost complete healing at the end of the fourth week, after which time the patient failed to return for observation.

**CASE 3.**—A boy aged 12 years with epilepsy had been treated by an Indian doctor and had received enormous doses of bromide, estimated at 300 grains (20 Gm.) a day. The child presented a lesion on his left leg approximately 8 inches long and from 2 to 3 inches wide. There were several places of marked

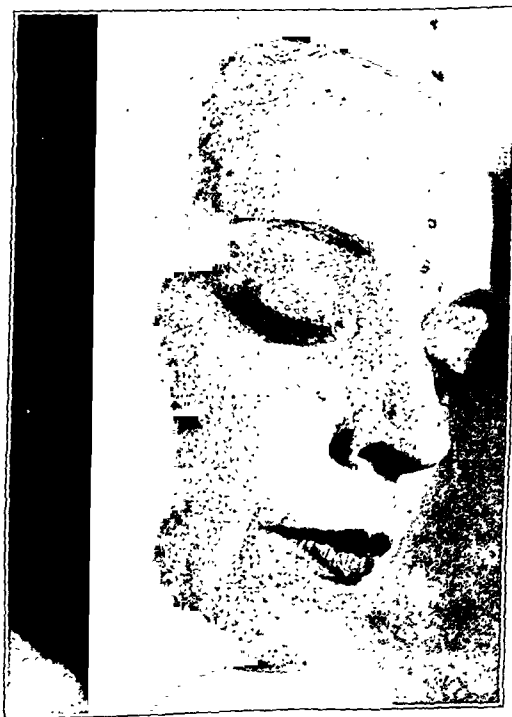


Fig. 2 (case 5).—Bromide eruption on face (blood serum bromide 137 mg. per hundred cubic centimeters).

became swollen, raised and papilliform and contained minute abscesses typical of bromide eruption (fig. 1). Other papular lesions developed on her face and back (fig. 2). The activity on the ankle was confined to the injured area. Her blood bromide level was 137 mg. per hundred cubic centimeters. She was treated with 10 Gm. of sodium chloride by mouth, 1 Gm. of sodium bicarbonate, and 5 cc. of adrenal cortex extract daily for six days. On the second day her blood bromide



level was 75 mg., the third day 60 mg., the fourth day 42 mg. and the twelfth day 18 mg. This lesion became more painful from the second to the fourth day. Healing was noticeable at the end of the second week, and the skin was smooth and apparently healed on the thirty-sixth day.

The ten persons observed with bromism were patients at the Central State Hospital and consisted of five selected women and five selected men with an average age of 27, all in apparently good general health except for their mental symptoms. Most of these patients had taken bromides on previous occasions but none had had any for two months. Three of the men were dropped from the list because of problems of management encountered in hospitals for the insane. Their cases were incomplete and were dropped from the report. An initial determination of the level of the bromide and chloride of the blood were done on all patients. All were then started on bromide alone, the dosage being from 60 to 120 grains (4 to 8 Gm.) daily, given in an effort to build up the bromide level of the blood. The retained bromides were seen to be in direct ratio to the amount given. When the serum bromides were reaching the toxic level the patients were divided, and three of the women were treated by being given chloride and adrenal cortex extract in conjunction, and two were treated by being given chloride alone. One of the men was given chloride and adrenal cortex extract, and the other chloride alone. This treatment consisted of 10 Gm. of sodium chloride by mouth and 5 cc. of adrenal cortex extract intramuscularly daily to four patients (three women and one man) and the others (two women and one man) received only 10 Gm. of sodium chloride daily. The patients receiving the chloride alone had treatment continued longer than the others, as indicated in table 2. Two of the women broke out with mild bromide eruptions. Of the three patients who took chloride alone, two developed a rather marked edema of the feet and ankles near the end of the course. They were given sodium bicarbonate and were relieved rather promptly. There was no evidence in any of these cases of any kidney irritation (table 2).

#### CONCLUSIONS

From the foregoing data we conclude that:

1. Adrenal cortex extract when given in combination with sodium chloride is apparently of value in the excretion of bromide and bromide effects.
2. Trauma has an influence in bromide eruptions.
3. Sodium bicarbonate is of apparent value in controlling the edema seen in extensive chloride therapy.
4. Adrenal cortex extract restores the normal physiologic level of chloride.

412 Medical Arts Building.

#### ABSTRACT OF DISCUSSION

DR. EUGENE F. TRAUB, New York: I am delighted that the authors have presented a method of treatment that is such a distinct improvement in handling bromide eruptions. Undoubtedly this can be utilized in managing iodide eruptions as well. The authors must be doubly congratulated that they were the first to recognize the value of adrenal cortex extract for the prompt and effective relief of bromodermas. The administration of sodium chloride to subjects with Addison's disease has always exerted a beneficial effect, but since the development of adrenal cortex therapy our approach has been altered and we now have a much improved method of treatment. I believe that this paper paves the way for several problems which the authors should continue to carry on. First, I would suggest that, instead of stopping the bromides at a certain point, as they did in their

experiment, they continue with the use of bromides and further note the effect of adrenal cortex extract on a patient who is continuing both treatments. It is barely possible that the use of adrenal cortex extract may make it possible for us to give much larger and more effective doses of both bromides and iodides without harmful effect. The second problem that they might attempt would be to study the effect of adrenal cortex extract alone without the use of sodium chloride. As a check on this they might study the effect of using sodium chloride while giving bromides. And, as a further check, they might observe the effect of using no medication and note the rate of return of the blood levels to normal. The authors also found that in their cases there was no kidney irritation. This may have been due to the fact that they were studying healthy young subjects, or it may be possible that the failure to note kidney irritation may have been due to the use of adrenal cortex extract. I believe that point should be investigated further.

DR. E. W. ABRAMOWITZ, New York: The neurologists are undecided as to which is more effective as a sedative, the barbiturates or the bromides. This paper is exceedingly appropriate in this regard. The finding of an increased amount of bromide in the serum and in the urine is of importance in the prevention of bromide intoxication. Anything above 75 mg. per hundred cubic centimeters of bromide in the serum may be a sign of impending trouble. However, there are persons in whom the bromides reach much higher levels and no signs of intolerance develop. This is particularly true of those who develop cutaneous eruptions. It is well known that there is only a small proportion of those with mental bromidism who present bromodermas. It is apparent, therefore, that there are other factors besides bromide retention in those with cutaneous eruptions. These factors are individual susceptibility and trauma, among others. I recently presented a patient before the Manhattan Dermatological Society (*Arch. Dermat. & Syph.* 40:478 [Sept.] 1939) who, while getting insulin injections, was given some bromide to take and she promptly developed a bromoderma at the sites of the injections of insulin. It is known that a decompensated adrenal insufficiency is associated with a constant decrease in the concentration of sodium in the blood. This is accompanied by a corresponding drop in the chlorides. The use of sodium chloride instead of adrenal cortex extract may be more economical in controlling bromide retention in the body. Loeb (*Bull. New York Acad. Med.* 16:347 [June] 1940) advocated the use of desoxycorticosterone esters 1 to 10 mg. daily in adrenal cortical insufficiency. This is a synthetic preparation said to be more active than adrenal cortex extract.

DR. RICHARD L. SUTTON JR., Kansas City, Mo.: The authors have hit on an ingenious method which does the job. Another way of reducing blood bromide concentration was suggested to me by Dr. Ralph Major, of the University of Kansas, who removes gastric juice which is normally rich in chloride and in brominism is rich in bromide. Continuous suction of gastric secretion, replacing chloride by intravenous drip, will reduce blood bromide concentration dramatically and perhaps lower it 50 per cent in twelve hours. As for the level in the blood which is associated with symptoms, not necessarily cutaneous but really mental intoxication, I have seen two physicians with chronic pruritic dermatoses in whom the bromide levels at onset of symptoms were only about 50 and 70 mg. per hundred cubic centimeters. I have become reluctant to prescribe bromides.

DR. C. P. BONDURANT, Oklahoma City: I want to express appreciation for the assistance of Drs. Brake and Prosser of the Central State Hospital for helping me carry out this work on these epileptic patients. Time will not allow us to discuss all the points brought up. I would call attention to the scratch mark in case 5, in which the bromide eruption appeared in the traumatized area. I think it was Ingram and Muck who in 1906 first called attention to the fact that trauma was a factor in the location of bromide eruptions. To my knowledge, this is the first picture which exemplifies rather conclusively this fact. I wanted to produce some scratch marks on these epileptic patients but met with objections which precluded this possibility. Dr. Traub points out further work which would more conclusively establish this principle of therapy in bromide retention. We intend to continue this work along many of the lines he discussed. I am not sure whether the adrenal cortex extract

was a factor in reducing kidney irritation in the epileptic patients studied. These patients were selected particularly because they were in good health, and previous hospital records showed no evidence of kidney irritation. The question of bromide levels in bromide intoxication and bromide eruption is a large subject. I believe there is a personal element which enters into each of these cases, with reference to this type of intoxication and eruption, and is the same as the personal element seen in other forms of intoxication from alcohol and other things.

## THE EFFECTS OF INTRAVENOUS SOLUTIONS ON PATIENTS

WITH AND WITHOUT CARDIOVASCULAR DEFECTS

FRANCIS D. MURPHY, M.D.

HOWARD CORRELL, M.D.

AND

JOHN C. GRILL, M.D.

MILWAUKEE

The popularity of giving fluids intravenously is growing, and the benefits derived from them are generally well known. Through the investigations of many workers<sup>1</sup> the indications for the various solutions have been satisfactorily worked out, but the contraindications to their use, because of possible harmful side effects on the various systems of the body, have not been as well established. Clinical observations have convinced us that the use of fluids intravenously has been too promiscuous and has been responsible for serious complications.

In this study we have attempted to determine the effect of different fluids on tests of cardiovascular function, particularly with reference to the ability of the cardiovascular system to accommodate the added fluids. It was our hope to be able to establish a simple method of forecasting the tolerance of the cardiovascular system for intravenous fluids, but this hope was not fulfilled.

Elderly persons without heart disease and cardiac patients with and without heart failure were studied. Intravenous administration alone was employed because of its generally increased popularity, easy control, freedom from pain and certainty of introduction.

The observations included changes in the blood and plasma volume, red count, hematocrit, plasma protein, hemoglobin, pulse, blood pressure, respiration, venous pressure, arm to lung and arm to tongue circulation time, vital capacity, electrocardiograms and minute vol-

ume urinary output at fifteen to thirty minute intervals for one-half hour before, during and two to four hours thereafter. The patients were weighed at intervals before and after. To 10 noncardiac patients between 60 and 75 years of age with serious organic disease such as carcinoma and surgical gallbladder disease 1,000 cc. of fluid, either physiologic solution of sodium chloride or 5 per cent dextrose solution in water, were given intravenously at various rates of speed three times daily for a continuous period of three days. None of these patients were obviously dehydrated or had serious renal disease. Four hours prior to fluid administration and throughout the entire test period, enteral feeding was prohibited. To both the cardiac and noncardiac patients the fluids were given at rates which we found to be used in many hospitals in this country. As our purpose was to test the tolerance of the cardiovascular system to the rate and volume of fluid, therapeutic indications were not demanded nor were volumes assumed to be safe always employed. The fluids used, rate of injection and classification of the patients are indicated in table 1.

### METHODS

The total blood and plasma volumes were calculated from the body surface area, plasma protein and hematocrits, by the method (method A) described by Gilligan and Altschule.<sup>2</sup> The total plasma protein was deter-

TABLE 1.—Type of Fluid, Volume, Rate of Injection per Minute and Cardiac Classification

Fluid	Vol- ume, Cc.	Rate per Minute, Cc.	Non- Cardiac	Cardiac				Total
				1&2	3	4		
Physiologic solution so- dium chloride .....	1,000	25-35	64	12	..	1		77
Physiologic solution so- dium chloride .....	2,000	35-45	2	1	..	..		3
5% dextrose in water....	1,000	25-35	17	5	..	..		23
10% dextrose in water....	1,000	20-35	2	5	6	4		17
20% dextrose in water....	1,000	15-20	1	..	1	..		2
50% dextrose in water....	200	10-20	..	3	5	6		14
50% dextrose, 8 grains of aminophylline .....	200	10-20	..	2	5	6		13
50% dextrose, 8 grains of aminophylline .....	50	10-20	1	2	2	6		11
			87	30	19	23		159

mined by the gravity method of Kagan<sup>3</sup> and checked frequently by refractometric methods and the method of Kjeldahl. These values were further checked by hemoglobin determinations with a Klett photoelectric colorimeter and red cell counts. The venous pressure was measured by the direct sodium citrate method with a B-D manometer. Ether was used in determining the arm to lung time by the technic described by Hitzig<sup>4</sup> and checked occasionally with paraldehyde.<sup>5</sup> Decholin (6 cc. of 20 per cent solution) was used in determining the arm to tongue time. For these three tests the arm was in a resting position at about a 60

From the Marquette University School of Medicine, and Clinics, Milwaukee County Hospital.

Read before the joint meeting of the Section on Practice of Medicine and the Section on Pharmacology and Therapeutics at the Ninety-First Annual Session of the American Medical Association, New York, June 14, 1940.

1. These investigations have been reported by:

- Seibert, F. B.: Fever-Producing Substances Found in Some Distilled Waters, *Am. J. Physiol.* **67**: 90 (Dec.) 1923; Cause of Many Febrile Reactions Following Intravenous Injections, *ibid.* **71**: 621 (Feb.) 1925.  
Hort, E. C., and Penfold, W. J.: The Dangers of Saline Injections, *Brit. M. J.* **2**: 1589, 1911; A Critical Study of Experimental Fever, *Proc. Roy. Soc., London, S. B.* **85**: 174, 1912; Micro-Organisms and Their Relation to Fever, *Proc. Path. Soc. Great Britain & Ireland* **17**: 109, 1912-1913.  
Bourn, J. M., and Seibert, F.: Cause of Many Febrile Reactions Following Intravenous Injections, *Am. J. Physiol.* **71**: 652 (Feb.) 1925.  
Rademaker, Lee: The Cause and Elimination of Reactions After Intravenous Infusions, *Ann. Surg.* **92**: 195 (Aug.) 1930; Reactions After Intravenous Infusions: A Further Report on Their Elimination, *Surg., Gynec. & Obst.* **56**: 956 (May) 1933.  
Elser, W. J., and Stillman, R. G.: The Fetish of Triply Distilled Water, *J. A. M. A.* **100**: 1326 (April 29) 1933.  
Coller, F. A., and Maddock, W. G.: The Water Requirements of Surgical Patients, *Ann. Surg.* **98**: 952 (Nov.) 1933; A Study of Dehydration in Humans, *ibid.* **102**: 947 (Nov.) 1935.  
Coller, F. A.; Dick, V. S., and Maddock, W. G.: Maintenance of Normal Water Exchange with Intravenous Fluids, *J. A. M. A.* **107**: 1522 (Nov. 7) 1936. Coller, F. A., and Maddock, W. G.: Water and Electrolyte Balance, *Surg., Gynec. & Obst.* **70**: 340 (Feb., no. 2A) 1940.

2. Gilligan, D. R.; Altschule, M. D., and Volk, M. D.: Effects on the Cardiovascular System of Fluids Administered Intravenously in Man: Studies of the Amount and Duration of Changes in Blood Volume, *J. Clin. Investigation* **17**: 7 (Jan.) 1938.

3. Kagan, B. M.: A Simple Method for the Estimation of Total Protein Content of Plasma and Serum: II. The Estimation of Total Protein Content of Human Plasma and Serum by the Use of the Falling Drop Method, *J. Clin. Investigation* **17**: 373 (July) 1938.

4. Hitzig, W. M.: Measurement of Circulation Time for Antecubital Veins to Pulmonary Capillaries, *Proc. Soc. Exper. Biol. & Med.* **31**: 935 (May) 1934.

5. Candel, Samuel: Determination of the Normal Circulation Time from the Antecubital Veins to the Pulmonary Capillaries by a New Technic, *Ann. Int. Med.* **12**: 236 (Aug.) 1938. Manchester, Benjamin: Measurement of Velocity of Blood Flow from Arm to Lung by Use of Paraldehyde (Preliminary Report), *M. Ann. District of Columbia* **8**: 49 (Feb.) 1939.

degree angle, the antecubital vein being 4 cm. below the fourth costosternal junction. The vital capacity was measured in cubic inches by means of a Simplex spirometer. The bladder was catheterized and urine collected at suitable intervals before, during and after fluid injection for calculation in cubic centimeters output per minute. The subjective and objective changes in the patients' condition were also noted.

## RESULTS

*Plasma Volume.*—The average changes in total calculated plasma volume with the fluids in the different

of fluid administered, regardless of the rate. With 5 per cent dextrose solution the increase is only 100 cc., or one-tenth the volume of fluid administered.

2. With hypertonic solutions the changes are of the same character, but, while the original increase is greater in proportion to amount of fluid given, it is less in proportion to amount of solute, the rise is less sustained, and by the end of four hours the plasma volume is usually below control levels.

3. The addition of aminophylline greatly diminishes the initial increase or causes an actual initial decrease in total calculated plasma volume.

4. The greater the degree of cardiac decompensation, the less the initial increase in plasma volume.

TABLE 2.—Changes in the Plasma Volume Immediately After and One-Half, One, Two and Four Hours After the Various Fluids Given Intravenously to Cardiac and Noncardiac Patients

Fluid	Number of Cases	Classification	Rate per Minute Cc.	Immediately After, Cc.	One-Half Hour, Cc.	One Hour, Cc.	Two Hours, Cc.	Four Hours, Cc.
1,000 cc. 5% dextrose in water.....	18	Noncardiac	20-30	+310	.....	.....	+100	+100
1,000 cc. physiologic solution sodium chloride...	40	Noncardiac	20-30	+310	+220	+240	+245	+180
	39	Noncardiac	30-40	+440	+240	+330	+215	+185
2,000 cc. physiologic solution sodium chloride...	3	Noncardiac	30-40	+630	+465	.....	+240	+200
200 cc. 50% dextrose in water.....	9	Groups 2 & 3 cardiac	10-15	+230	+20	+145	+90	—60
	6	Group 4 cardiac	10	+185	+45	+45	+145	.....
200 cc. 50% dextrose, 8 grains of aminophylline	6	Groups 2 & 3 cardiac	10	+45	—70	—80	—50	—205
	6	Group 4 cardiac	10	—50	—255	—220	—70	—75
50 cc. 50% dextrose, 8 grains of aminophylline	4	Groups 2 & 3 cardiac	10	+30	—50	—125	—20	—30
	6	Group 4 cardiac	10	+10	—95	—115	—85	—60
1,000 cc. 10% dextrose in water.....	4	Noncardiac	20-25	+225	+25	.....	+25	+35
	7	Groups 1, 2 & 3 cardiac	20-25	+165	—80	+15	+90	—40
	4	Group 4 cardiac	10-20	+20	—80	+40	+145	—70
Total.....	152							

TABLE 3.—Average Changes in the Venous Pressure Immediately After, One-Half, One, Two, and Four Hours After the Various Fluids Given Intravenously at the Stated Rates to Cardiac and Noncardiac Patients

Fluids	Number of Cases	Patient's Class of Compensation	Rate in Control, Cc. per Minute	Rate in Control, Mm. Water	During	Immediately After	One-Half Hour After	One Hour After	Two Hours After	Four Hours After
1,000 cc. 5% dextrose in water.....	20	Noncardiac	30-50	62	....	+20	....	....	+4	—10
1,000 cc. physiologic solution sodium chloride...	33	Noncardiac	20-30	66	....	+24	0	—2	+8	—16
	24	Noncardiac	30-40	48	....	+11	—5	+2	....	0
2,000 cc. physiologic solution sodium chloride...	3	Noncardiac	30-40	73	+40	+70	+20	....	+16	+35
200 cc. 50% dextrose in water.....	9	Groups 2 & 3 cardiac	7-15	96	....	+24	+11	+8	+2	+50
	6	Group 4 cardiac	7-15	180	....	+13	—18	—9	—17	—20
200 cc. 50% dextrose, 8 grains aminophylline..	5	Groups 2 & 3 cardiac	7-16	110	+31	+37	+6	+11	....	+5
	6	Group 4 cardiac	7-10	177	—11	—2	—20	—24	—8	+10
50 cc. 50% dextrose, 8 grains aminophylline..	4	Groups 2 & 3 cardiac	5-10	115	—10	+6	+7	+4	....	—8
	6	Group 4 cardiac	5-10	190	—20	—30	—44	—56	—60	—30
1,000 cc. 10% dextrose in water.....	4	Noncardiac	20-25	80	....	0	—2	....	....	—15
	7	Groups 1, 2 & 3 cardiac	20-25	88	....	+30	+12	+7	....	+10
	4	Group 4 cardiac	10-20	145	....	+60	+14	0	....	+3
Total.....	141									

types of patients at stated intervals after injection are given in table 2. We may briefly summarize these changes by saying:

1. One thousand cc. of physiologic solution of sodium chloride or 5 per cent dextrose solution at 20 to 30 cc. per minute in noncardiac patients causes:

(a) An average increase in total calculated plasma volume of 310 cc. within the first one-half hour of starting fluids; that is, an increase of one-third the volume of fluid given.

(b) Increasing the rate of injection causes a parallel increase in total calculated plasma volume.

(c) Increasing the volume of solution causes an increase which is not in direct proportion.

(d) Within one-half hour, the increase in plasma volume falls one third. The rate of fall is directly proportional to the speed with which the physiologic solution of sodium chloride is given.

(e) At the end of four hours there is an increase of 200 cc. in total calculated plasma volume, or about one-fifth the volume

5. Repeated administration of 1,000 cc. of physiologic solution of sodium chloride causes a gradual increase in plasma volume. This is obviated by the occasional use of 5 per cent dextrose solution interspersed with the physiologic solution of sodium chloride.

*Blood Volume.*—The total calculated blood volume changes with isotonic solutions approximated the plasma volume changes in pattern and kept the same approximate relationship throughout. With hypertonic solutions the changes were highly inaccurate, owing in part to actual shrinkage of the red cell size leading to inaccurate hematocrit readings for the calculations. Blood volume is not reported for this reason.

*Venous Pressure.*—Changes in venous pressure for the same groups are given in table 3. We may summarize these changes by saying:

1. The venous pressure changes in general parallel the plasma volume changes.

2. In general, the higher the initial venous pressure, the less pronounced the rise after fluid administration.

3. The onset of acute failure of the left side of the heart was not always associated with a change in venous pressure. Two of four patients going into acute left ventricular failure showed a slight decrease in venous pressure while in acute failure.

4. The venous pressure never rose to pathologic levels (over 120 mm. of water) unless failure was present or occurred during administration of fluid.

5. The initial increase with physiologic solution of sodium chloride and hypertonic dextrose solution, previously noted by several other workers,<sup>6</sup> persisted for from forty to sixty minutes and was then followed by a fall in venous pressure, usually without regard to the continued administration of fluids.

6. Only in solutions with aminophylline was there an initial decrease in venous pressure. This has been reported by Greene, Paul and Feller.<sup>7</sup>

7. There was no difference in the character of venous pressure response between valvular and nonvalvular heart disease, or between patients with compensated heart disease and normal persons except for differences in height.

**Circulation Time.**—In 34 noncardiac persons the initial decholin time ranged from 11.8 seconds to 30.2 seconds, the average being 19.6 seconds. The ether time in these patients ranged from 6.6 seconds to 21.2 seconds and averaged 11.2 seconds. Those with circu-

nificant decrease in the vital capacity at times on taking fluids, though clinically improved, and at other times a significant increase with clinical evidence of increasing failure.

**Pulse, Respiration and Blood Pressure.**—In common with almost all other workers, we found no significant or constant changes in the pulse or respiration of cardiac and noncardiac patients on fluid administration regardless of the rate, volume or type of fluid, except those patients with heart failure made worse, or going into acute left ventricular failure, when an increase usually occurred. Except with 1,000 cc. of 10 per cent dextrose in water, wherein increase in blood pressure was usually noted during and one hour after administration, there was no significant change in blood pressure, unless heart failure ensued or became worse.

**Electrocardiograms.**—Electrocardiograms were taken in 58 cases. There was no change in 72.4 per cent of our cases. A decrease in QRS voltage returning to normal at the end of four hours occurred in 5.2 per cent and a decrease in QRS not returning to normal in four hours in 3.45 per cent. Increase of QRS voltage persisting after four hours, persistently negative T<sub>s</sub>, gain in T<sub>s</sub> and T<sub>1</sub> voltage and bigeminal rhythm occurred once each. There was no correlation between response of the cardiovascular system to fluids and electrocardiographic changes. No constant electrocardiographic changes were produced in our cases.

**Urinary Output.**—The average six hour urinary output for the different types of patients is shown in table 4.

1. Diuresis was greatest in those cases of marked edema in which the kidney function was normal. Therefore, in rheumatic and syphilitic heart disease with congestive failure the diuresis was greater than in hypertensive and arteriosclerotic heart disease with the same amount of congestive failure.

2. With 5 per cent dextrose in water, the greatest diuresis occurred and in six hours about equaled the intake of fluid.

3. With 5 per cent dextrose in saline solution the diuresis was about one-half that for 5 per cent dextrose in water.

4. With physiologic solution of sodium chloride the diuresis was less than half that for 5 per cent dextrose in water.

5. Hypertonicity of the dextrose solution increased the diuresis, and the addition of aminophylline further increased the diuresis.

6. The onset of diuresis in general coincided with the fall in plasma volume and venous pressure.

**Clinical Changes.**—One hundred per cent of the group 4 cardiac patients given 1,000 cc. of 10 per cent dextrose were made worse, 66 per cent of the group 4 patients given 200 cc. of 50 per cent dextrose with 8 grains (0.5 Gm.) of aminophylline were made worse, and 40 per cent of those given 200 cc. of 50 per cent dextrose in water were made worse.

Of 19 cardiac patients in group 3 compensation, 15.8 per cent were made worse when given fluid in volumes of 200 cc. or more.

In the cardiac patients of groups 1 and 2 compensation and all the noncardiac persons, no constant change in clinical condition was noted except for the development of pitting edema and weight gain in 50 per cent of those receiving 3,000 cc. of physiologic solution of sodium chloride daily for three days.

TABLE 4.—Average Six Hour Urinary Output

	1,000 Cc. Physio- logic Solution of Sodium Chloride, Cc.	1,000 Cc. 5% Dex- trose, Cc.	1,000 Cc. 10% Dex- trose, Cc.	200 Cc. 50% Dex- trose, Cc.	200 Cc. 50% Dex- trose with 8 Gr. Amino- phylline, Cc.	50 Cc. 50% Dex- trose with 8 Gr. Amino- phylline, Cc.
Grade 4.....	...	...	350	545	755	825
Grade 3.....	...	...	804	320	805	...
Grade 2.....	...	...	...	490	1140	780
Grade 1.....	...	...	898	...	...	200
Noncardiac.....	412	900	...	...	...	...

lation time longer than 20 seconds for decholin, or 10 seconds for ether, were all in the age group over 60 and had evidence of grave extracardiac disease.

The noncardiac persons with initial normal circulation time and the cardiac patients with normal or prolonged circulation time usually had an initial increase in both decholin and ether times followed within one hour by a decrease below the initial time, which persisted for four hours. There was little difference in the extent or direction of change with the volumes employed, the rate of injection, composition of the solution or degree of cardiac compensation. The noncardiac persons with prolonged initial circulation time had an initial decrease in the circulation time to within normal limits persisting for four hours.

**Vital Capacity.**—An increase or decrease of more than 5 per cent was considered significant. All our noncardiac patients showed no significant change in vital capacity with administration of fluid. Cardiac patients with different degrees of compensation showed a sig-

6. Altschule, M. D., and Gilligan, D. R.: The Effects on the Cardiovascular System of Fluids Administered Intravenously in Man: II. The Dynamics of the Circulation, *J. Clin. Investigation* 17: 401 (July) 1938. Caughey, J. L.: The Effect of Rapid Infusion on Venous Pressure: A Test of Cardiac Reserve, *Proc. Soc. Exper. Biol. & Med.* 32: 973 (March) 1935. Richards, D. W.; Caughey, J. L.; Courmand, André, and Chamberlain, F. L.: Intravenous Saline Infusion as a Clinical Test for Right-Heart and Left-Heart Failure, *Tr. A. Am. Physicians* 52: 250, 1937. Meek and Eyster.<sup>8</sup> Eyster and Middleton.<sup>9</sup>

7. Greene, J. A.; Paul, W. D., and Feller, A. E.: Action of Theophylline with Ethylenediamine on Intrathecal and Venous Pressures in Cardiac Failure and on Bronchial Obstruction in Cardiac Failure and in Bronchial Asthma, *J. A. M. A.* 109: 1712 (Nov. 20) 1937.

## COMMENT

From our results it appears that these tests of cardiovascular function cannot be relied on to determine preclinical evidence of unfavorable response of the cardiovascular system to fluids. The careful clinical examination of the patient with regard to the condition of the cardiovascular system remains the most important safeguard in determining the type, quantity and speed of intravenous infusions.

The introduction of fluid intravenously will cause an initial increase in plasma volume, blood volume and venous pressure. These initial increases are fairly constant for the type of fluid, rate of administration and degree of cardiac compensation. They persist for a period of thirty to forty minutes and then, regardless of continued introduction of fluid, tend to fall.

If the decrease were in venous pressure alone, vasodilatation as proved by Meek and Eyster<sup>8</sup> and Eyster and Middleton<sup>9</sup> could be the explanation. The coincidental fall in plasma and blood volumes, however, necessitates the consideration of additional factors. By utilizing weight changes and urinary excretion, some of these additional factors can be illustrated.

In solutions with aminophylline and hypertonic dextrose solution, the changes are mainly due to increased elimination through the kidneys.

With physiologic solution of sodium chloride, urinary excretion is insufficient to account for the changes and other mechanisms must be sought. Jacobs and Colwell<sup>10</sup> and Cutting, Lands and Larson<sup>11</sup> have shown that excretion through the gastrointestinal tract and increased intracellular and extracellular water deposition are important with isotonic and hypertonic salt solutions. As the patients gained weight despite the small increase in plasma volume, extracellular water deposition must be assumed.

The less marked increase of plasma and blood volume in cardiac decompensation with less pronounced rise in venous pressure and decreased urinary excretion suggest more rapid loss of fluid from the vascular system into the extracellular or intracellular depots. This rapid loss may be due to (1) a mechanical defect, the increased venous pressure preventing reabsorption at the venous end of the circuit; (2) tissue injury with loss of intracellular potassium increasing the osmotic tension of the extracellular fluid as suggested by Scudder;<sup>12</sup> (3) injury to the capillary wall with increased loss of protein, which seems unlikely in view of the elevated plasma protein, or (4) some other chemical alteration of the intravascular or extravascular fluid upsetting the osmotic equilibrium.

From our studies we have shown that the venous pressure is not always sufficiently elevated to be the sole cause of the well known hemoconcentration occurring in heart failure or the decreased plasma and blood volume changes observed in our patients going into failure. By inference, then, one of the other chemical changes must be suspected.

It appears from this that the distribution of the fluid in the various systems and the proportionate importance

of the different routes of elimination is dependent on the type and concentration of the solution, degree of cardiac compensation, integrity of renal function, state of hydration of the patient, mechanical factors of venous pressure changes and changes in the chemical constituents of the tissues and tissue fluids.

In considering circulation time, the normal values for arm to tongue time have been found to be between 10 and 16 seconds, averaging 13 seconds.<sup>13</sup> The normal values for ether in the arm to lung time have been found to vary between 3 and 8 seconds with an average of 5.5 seconds.<sup>14</sup> Prolongation of arm to tongue time beyond 20 seconds or arm to lung time beyond 10 seconds has been assumed to be indicative of left, right or total heart failure, in the absence of polycythemia or reduced metabolic rate. The frequent occurrence of much higher values in our elderly patients without heart disease, but with other serious organic disease, is contrary to expectations and has not been explained. It must be remembered that the use of these tests is not an accurate index of the velocity of circulation between two points (1) because the velocity of blood flow is not constant in all parts of a single vessel, the axial stream, composed of solid elements, being faster than the peripheral plasma; (2) because the velocity of flow of the injected solution is different than the velocity of the blood; (3) because the velocity of flow is dependent on the diameter of the vessel which is not constant, and (4) because of the reaction time<sup>15</sup> of the individual, which is not known to be constant. This complicated relationship of decholin and ether time to velocity of blood flow would in itself make the test of little value in determining preclinical evidences of cardiovascular failure.

The vital capacity is not a satisfactory test for determining preclinical changes in the cardiovascular system, apparently because factors other than pulmonary congestion and edema play a part in the production of dyspnea. Cooperation of the patient, anoxia of the medullary respiratory center, increased intracranial pressure and changes in the coronary flow have been postulated as extrapulmonary causes of dyspnea.

Our failure to find significant changes in the electrocardiogram which would be of assistance in determining the onset of failure corroborates the absence of significant changes found by Miller and Poindexter<sup>16</sup> in dogs.

The clinical observation that 50 per cent of group 4 cardiac patients, from 20 to 50 per cent of group 3 cardiac patients and occasional group 2 cardiac patients are made worse by from 100 to 200 cc. of 50 per cent dextrose solution, with or without 8 grains (0.5 Gm.) of aminophylline, suggests that this volume of fluid often advocated in the treatment of acute left ventricular

8. Meek, W. J., and Eyster, J. A. E.: The Effect of Plethora and Variations in Venous Pressure in Distal Size and Output of the Heart, *Am. J. Physiol.* **61**: 186 (June) 1922.

9. Eyster, J. A. E., and Middleton, W. S.: Cardiovascular Reactions to Hemorrhage and Transfusions in Man, *ibid.* **68**: 581 (May) 1924.

10. Jacobs, H. R., and Colwell, A. R.: Lesions in the Pancreas and in the Anterior Hypophysis with Fatal Acidosis Following Prolonged Intravenous Administration of Glucose (in Dogs), *Am. J. Physiol.* **116**: 194 (June) 1936.

11. Cutting, R. A.; Lands, A. M., and Larson, Paul S.: Distribution and Excretion of Water and Chlorides After Massive Saline Infusions, *Arch. Surg.* **36**: 886 (April) 1938.

12. Scudder, John: Shock: Blood Studies as a Guide to Therapy, Philadelphia, J. B. Lippincott Company, 1940.

13. Tarr, Leonard; Oppenheimer, B. S., and Sager, R. V.: The Circulation Time in Various Clinical Conditions Determined by the Use of Sodium Dehydrocholate, *Am. Heart J.* **8**: 766 (Aug.) 1933. Haer, Samuel, and Slipkoff, Bernard G.: Measurement of Circulation Times and Agents Used in Their Determination, *Am. Heart J.* **16**: 29 (July) 1938. Fishberg, A. M.; Hitzig, W. M., and King, F. H.: Measurement of Circulation Time with Saccharin, *Proc. Soc. Exper. Biol. & Med.* **30**: 651 (Feb.) 1933. Webb, George; Sheinfeld, William, and Colin Hyman: Importance in Surgery of Blood Circulation Time, *Ann. Surg.* **104**: 460 (Sept.) 1936. Lian, C., and Faquet, J.: La mesure de la vitesse circulatoire avec l'éther, la saccharine et la fluorescéine dans les principaux types d'insuffisance cardiaque, *Bull. et mém. Soc. méd. d. hôp. de Paris* **52**: 428 (March 23) 1936. Goldberg, S. J.: Use of Calcium Gluconate as Circulation Time Test, *Am. J. M. Sc.* **192**: 36 (July) 1936.

14. Hitzig, W. M.; King, F. H., and Fishberg, A. M.: Circulation Time in Failure of Left Side of Heart, *Arch. Int. Med.* **55**: 112 (Jan.) 1935. Hitzig.

15. Kvale, W. F., and Allen, E. V.: Rate of Circulation to Arteries and Veins of Man: Studies of Normal Subjects and of Those with Occlusive Arterial Disease and Hyperthyroidism, *Am. Heart J.* **18**: 519 (Nov.) 1939.

16. Miller, J. R., and Poindexter, C. A.: The Effects Observed Following the Intravenous and Subcutaneous Administration of Fluid, *J. Lab. & Clin. Med.* **18**: 287 (Dec.) 1932.

failure<sup>17</sup> is unsafe, and volumes not greater than 50 cc. should be used.

#### CONCLUSIONS

1. No tests of cardiovascular function, so far known, will enable us to determine beforehand that the patient will respond unfavorably to fluids administered intravenously.

2. Careful clinical examination to determine the presence or absence of heart disease is still the best preventive for unfavorable reactions to fluid.

3. In the presence of heart disease, regardless of the state of compensation, fluids must be given slowly, in small volumes, preferably isotonic and repeated at intervals of not less than four to six hours.

4. These tests of cardiovascular function showed few constant changes even with the precipitation of heart failure.

5. Fifty per cent dextrose solution, with or without 8 grains (0.5 Gm.) of aminophylline, in volumes of 100 cc. or more, at rates of 10 cc. a minute, are extremely dangerous when used in treatment of heart failure, making from 50 to 100 per cent of the patients worse and precipitating failure in 20 per cent of grade 3 cardiac patients.

6. Fifty per cent dextrose solution with 8 grains of aminophylline in doses of 50 cc. improved the dyspnea of cardiac failure in all our cases, decreased the venous pressure and increased the urinary output.

7. The danger of fluid injection in cardiac patients may not be in increasing blood volume per se but rather in further altering the already disturbed chemistry of the body fluid, thus increasing osmotic pressure derangements.

8. The ultimate fate and mode of distribution or loss of injected fluid is dependent on the kind and concentration of the solution, state of hydration of the patient, degree of cardiac compensation, level of venous pressure and chemistry of body tissues influencing osmotic pressure.

9. Physiologic solution of sodium chloride may prove more useful in increasing blood volume than hypertonic solutions.

10. Noncardiac patients in the older age groups tolerated fluids as substitution therapy, in amounts up to at least 3,000 cc. daily in 1,000 cc. doses at rates of from 20 to 40 cc. per minute, even in the absence of dehydration.

11. Alternation of dextrose with the physiologic solution of sodium chloride obviated the changes in blood dilution, weight gain and occult or visible edema occurring with physiologic solution of sodium chloride alone.

12. The indiscriminate use of intravenous fluids, especially for persons with any cardiovascular defect, should be discouraged and the safeguards suggested be more strictly adhered to.

507 Carpenter Building.

#### ABSTRACT OF DISCUSSION

DR. N. C. GILBERT, Chicago: None of us doubt the value of parenteral fluid under certain conditions, such as dehydration, in certain cases of shock, or the use of moderate amounts postoperatively in cases in which there are definite indications. But many clinicians have felt that fluids were administered

unnecessarily and in too large amounts and that not infrequently there were harmful results. There has been little in the way of concrete evidence on which conceptions of indications or contraindications might be based. This paper has afforded definite evidence that harmful results may ensue from the use of fluids under certain conditions. A word of caution is timely. A few years ago Jones, Eaton and White published evidence on the subject which has not received the attention it merited. Their experimental work on animals complements the experimental clinical work of Dr. Murphy and his associates. It is valuable also because they could give large amounts of fluids without regard to an ultimate effect on the subject and were able to examine the tissues at immediate autopsy. Their experimental work was done on cats under various conditions, using 5 per cent dextrose solution or physiologic solution of sodium chloride in large amounts, but not larger than amounts frequently used clinically. They found that edema resulted not only in subcutaneous tissues but in the viscera as well. In the heart the increase in water content might amount to 4 or 5 per cent or even 10 per cent. Some of the factors influencing the occurrence of edema appeared to be nitrogen starvation, general malnutrition, sepsis, serous drainage, major surgical procedures and general anesthesia. That heart failure actually resulted in a large proportion of group III or group IV patients needs no comment, especially when it is considered that the amount of fluid used was rather moderate. The increase in plasma volume was definite. In a normal organism this could be taken care of readily by the kidney. But in cases in which the kidneys are unable to do their part it might devolve on the tissues to accommodate much of the excess fluid. If this was not done promptly the increase in blood volume would remain. If the tissue did take up the fluid, edema of the subcutaneous tissues or viscera would result to some degree.

DR. IRVING H. PAGE, Indianapolis: It has always been surprising to me that fluids are administered intravenously with but the slightest knowledge of the amount to give and only little greater knowledge of what clinical effects to expect. Drs. Murphy, Correll and Grill have exhibited a worthy curiosity in investigating this problem. Certain facts stand out clearly from this study: 1. There is no laboratory test which will predict unfavorable results from properly administered fluid. 2. Initial increase in blood volume and venous pressure occur, lasting from thirty to forty minutes, and then tend to disappear despite continued introduction of fluid. 3. Different fluids may be disposed of in different ways: (a) aminophylline and hypertonic dextrose solution chiefly by renal excretion. (b) physiologic solution of sodium chloride by the renal and gastrointestinal tract, and so on. 4. In cardiac decompensation the blood volume and venous pressure changes are less marked than normal, presumably because of more rapid loss of fluid into the intracellular space. 5. At least half of the patients with advanced left ventricular failure and one fourth of the less severe (group III) are made worse by amounts of 50 per cent dextrose over 100 cc. or 1 liter of isotonic dextrose solution regardless of whether or not aminophylline is given. Since many physicians have recommended much larger doses, this observation should be remembered. Lesser amounts appear to improve the dyspnea without necessary increase in vital capacity. Venous pressure decreases and diuresis occurs. The crux of the problem is that, when cardiac disease is present, fluids should be administered very slowly in amounts of not over 100 cc. for hypertonic and 1,000 cc. for isotonic solutions. This investigation emphasizes the importance of not giving fluids by vein in advanced cardiovascular disease without shock unless one has some specific purpose in mind. Unfortunately these purposes are not clearly defined. It is generally recognized that dextrose infusion is valuable when, because of vomiting, the patient is unable to take fluids by mouth. Second, it appears to decrease the severity of the dyspnea. Whether it is true that dextrose aids in the nutrition of the heart to the extent that it should be given intravenously seems to me very doubtful. Drs. Murphy, Correll and Grill have shown that administration of fluid in advanced cardiovascular disease has potential dangers and that, if given at all, it should be in small amounts, administered slowly.

17. Strauss, A. E.: Treatment of Myocardial Insufficiency, *M. Clin. North America* 20: 547 (Sept.) 1936. Smith, F. M.: Treatment of Left Ventricular Failure, *J. A. M. A.* 109: 646 (Aug. 28) 1937. Lyon, J. A.: The Diagnosis and Treatment of Cardiac Emergencies, *ibid.* 114: 835 (March 9) 1940. McMahon, Alphonse: Emergency Treatment of Acute Heart Failure, *ibid.* 113: 1025 (Sept. 9) 1939. Dry, T. J.: A Rationale for the Management of Heart Disease, *J. Iowa M. Soc.* 29: 236 (June) 1939.



THE USE OF ALUMINUM HYDROXIDE  
IN THE TREATMENT OF  
PEPTIC ULCER

A FOLLOW-UP STUDY OF 246 CASES

E. N. COLLINS, M.D.

CLEVELAND

C. P. PRITCHETT, M.D.

COLUMBUS, OHIO

AND

H. R. ROSSMILLER, M.D.

CLEVELAND

During the past four years, the use of colloidal aluminum hydroxide<sup>1</sup> has been included in the treatment of 470 patients having active peptic ulcer. Of 246 patients who had follow-up studies, satisfactory results were obtained in 88 per cent.

Judged by the relief of symptoms, the disappearance of formerly visualized ulcer craters, by progress roentgen examinations, and in the case of gastric ulcers by gastroscopic examinations as well, the immediate results of treatment compared favorably with those obtained by other forms of medical management.

However, since evaluation of treatment in this disease is difficult because of the factor of spontaneous remission, our chief purpose in this study was to appraise results in terms of the duration of these remissions.

Colloidal aluminum hydroxide has been substituted for the usual alkalis in the antacid therapy of peptic ulcer. It has advantages over the usual alkalis aside from its acid-combining power. In addition to its acid-combining power, its astringent and demulcent properties are of value. It does not liberate large quantities of carbon dioxide, as do the carbonates; it is not laxative, like the magnesium salts, and its use does not cause a compensatory stimulation of acid secretion like sodium bicarbonate. It is not absorbed and therefore can be given without the hazards of alkalosis, or precipitation of crystalline phosphates in an alkaline urine. In none of our cases has there been a disturbance of the acid-base balance or urinary complications.

The present view relative to its acid-combining power is that gastric secretions are inactivated to a  $pH$  compatible with the healing of pathologic tissue and that this action is reversed at the more alkaline levels of the duodenum, where the treated chyme continues to act as an acid.

Considering its neutralizing influence alone, Kirsner and Palmer<sup>2</sup> found that aluminum hydroxide was less effective than calcium carbonate, when determinations of the hydrogen ion concentration of gastric contents were made with a Beckman  $pH$  meter. They state "It is possible that the mere reduction in acidity from that of HCl to the acidity of an equimolar concentration of

aluminum chloride is adequate for the protection of the diseased area."

We have found that the free acidity of gastric contents can be continuously neutralized if sufficient quantities of aluminum hydroxide are given, using Topfer's reagent as an indicator. At the start of treatment in hospital patients, analyses of hourly aspirations during various twenty-four hour periods have been done in order to determine the correct dosage. However, after the first two weeks of treatment, smaller quantities of aluminum hydroxide have been used without detriment to the patients. At the present time we believe that properties other than its acid-combining power are at least of equal importance in explaining the satisfactory results obtained with this form of treatment.

## METHOD OF ADMINISTRATION

Analyses of the records in the present study show that no set routine was used in the administration of aluminum hydroxide. During the course of time changes have been made, but the object has been to formulate a plan which is flexible according to all features of the individual case.

One third of the 246 patients who used only medical management in this series had complications of duodenal ulcer, such as continued night secretion, or had gastric, multiple or marginal (anastomotic) ulcers with or without complications. Hospital management was used in the majority of these instances. In certain cases the continuous drip method of Winklestein,<sup>3</sup> developed by Woldman and Rowland,<sup>4</sup> was the method used in administering aluminum hydroxide. In other cases aluminum hydroxide was given orally during sleeping hours as well as during other hours. During the first week it was given at 12 midnight and at 2 and 4 a. m., usually in twice the dosage used during the daytime hours. During the second week of treatment, aluminum hydroxide was given at 12 midnight and 3 a. m. The amount used depended on analyses of hourly aspirations of gastric contents during two or more twenty-four hour periods of management.

Although gastric acidity was not completely and continuously neutralized during these periods, our aim was to keep the level of free acidity sufficiently low to prevent activation of pepsinogen, the proteolytic neutralization point emphasized by Hollander.<sup>5</sup>

Other modifications of the Sippy regimen,<sup>6</sup> similar to those used by Einsel, Adams and Myers<sup>7</sup> and by Woldman and Polan,<sup>8</sup> were used in these cases. Liquid petrolatum in 1 or 2 ounce (30-60 cc.) doses, and occasionally magnesium oxide or aromatic fluidextract of cascara sagrada, was given at bedtime to prevent constipation until the patient was including sufficient vegetables and fruit in his diet to assure proper bowel function.

If the clinical response of the patient was favorable, confirmed by progress roentgen examination and, in the case of gastric ulcer, also by gastroscopic examination,

Dr. Pritchett was formerly of the Cleveland Clinic.  
Read before the Section on Pharmacology and Therapeutics at the Ninety-First Annual Session of the American Medical Association, New York, June 13, 1940.

1. The preparation used by the patients in this study was either Amphojel, manufactured by John Wyeth & Brother Inc., of Philadelphia, or Creamalin, manufactured originally by the Cleveland Chemical Associates and now by the Alba Pharmaceutical Company, Inc., of New York, neither of which stand accepted by the Council on Pharmacy and Chemistry. Either preparation contains about 5 per cent of hydrated alumina and not more than 0.6 per cent of sodium chloride. It is a white, gelatinous substance, mildly astringent, nonirritating and amphoteric, with a  $pH$  of 6.9. It combines with twelve times its volume of tenth-normal hydrochloric acid within thirty minutes. The Council and the A. M. A. chemical laboratory are in process of elaborating standards for a suitable suspension of aluminum hydroxide.

2. Kirsner, J. B., and Palmer, W. L.: Effect of Various Antacids on the Hydrogen Ion Concentration of the Gastric Contents. *Am. J. Digest. Dis.* 7: 85-92 (March) 1940.

3. Winklestein, A.: A New Therapy of Peptic Ulcer: Continuous Alkaline Milk Drip into the Stomach. *Am. J. M. Sc.* 185: 695-703 (May) 1933.

4. Woldman, E. E., and Rowland, V. C.: New Technic for the Continuous Control of Acidity in Peptic Ulcer by the Aluminum Hydroxide Drip. *Am. J. Digest. Dis. & Nutrition* 2: 733-736 (Feb.) 1936.

5. Hollander, F.: What Constitutes Effective Neutralization of Gastric Contents? *Am. J. Digest. Dis.* 6: 127 (April) 1939.

6. Sippy, B. W.: Gastric and Duodenal Ulcer: Medical Cure by an Efficient Removal of Gastric Juice Corrosion. *J. A. M. A.* 64: 1625-1630 (May 15) 1915.

7. Einsel, I. H.; Adams, W. L., and Meyers, V. C.: Aluminum Hydroxide in the Treatment of Peptic Ulcer. *Am. J. Digest. Dis. & Nutrition* 1: 513-516 (Sept.) 1934.

8. Woldman, E. E., and Polan, C. G.: Value of Colloidal Aluminum Hydroxide in the Treatment of Peptic Ulcer. *Am. J. M. Sc.* 108: 155-164 (Aug.) 1939.

the use of aluminum hydroxide during sleeping hours was usually discontinued by the end of the second week. If it had been given hourly during waking hours, its administration was then changed to a two hour schedule, and ambulatory management as mentioned for uncomplicated duodenal ulcer was continued.

*Uncomplicated Duodenal Ulcer.*—Two thirds, or 154, of the patients in this series had uncomplicated duodenal ulcer. Most patients were ambulatory and they carried on with their usual occupation. Although the regimen advised was flexible according to severity of symptoms, in most instances the use of 2 drachms (4 Gm.) of aluminum hydroxide every two hours during waking hours for three months proved satisfactory. Either a meal or a glassful of milk was taken midway between doses of aluminum hydroxide. During the next three months a glassful of milk was taken midway between meals and 2 drachms of aluminum hydroxide was taken one hour after each meal, after each glassful of milk and at bedtime. During the remainder of the first year's treatment the taking of similar doses of aluminum hydroxide after the three main meals and at bedtime seemed to prove adequate.

It should be mentioned that certain patients having mild symptoms started treatment with three meals a day and a glassful of milk midway between meals, taking

TABLE 1.—*Peptic Ulcer Follow-Up Studies in 246 Cases*

	Number of Cases	Satisfactory Results	
		Cases	Per Cent
Duodenal ulcer, uncomplicated.....	154	150	97.5
Duodenal ulcer, massive hemorrhage.....	15	12	80.0
Duodenal ulcer, pyloric obstruction (temporary).....	12	12	100.0
Gastric ulcer (6 cases showed complications).....	37	33	89.0
Multiple ulcers, both gastric and duodenal..	8	6	75.0
Marginal ulcers, jejunal.....	7	5	71.0
Surgical cases (medical failures).....	13	0	0.0
Total.....	246	218	88.0

aluminum hydroxide one hour after each meal, after each glassful of milk and at bedtime. In an attempt to maintain a low gastric acidity and owing to the well known "ulcer diathesis" of patients having this disease, each patient is now instructed to take at least one feeding or a glassful of milk midway between meals for the remainder of his life.

If there is a history of seasonal recurrences, the patient is now advised to resume the two hour schedule of using aluminum hydroxide two weeks prior to the time of these recurrences each year, usually during the spring and fall, for a period of two months, over a five year period of time. The healing of any one peptic ulcer does not mean that the patient will not have another ulcer.

#### DIET

The diet has become more liberal since the use of aluminum hydroxide has been included as a part of management. The gain in weight of the average patient was as great on this management as was the case in other types of management. Three meals a day, consisting of the usual bland diet, were used at the start of treatment, and within the first week meat has been added. Ground meat was used at the start of treatment in cases of massive hemorrhage.<sup>9</sup> By the end of the second week vegetables and fruit in cooked form and

soon thereafter citrus fruit juices were included. The importance of a well balanced diet has been emphasized in all instances.

#### RESULTS OF TREATMENT

Nineteen patients having surgical procedures either had pyloric stenosis or used aluminum hydroxide only during postoperative management and so are not included in this follow-up study. However, another

TABLE 2.—*Uncomplicated Duodenal Ulcer, 154 Cases*

Duration	Continuous Remissions (Cases)	Recurrences of Symptoms (Cases)	Satisfactory Results, per Cent
2 to 11 months (64 cases).....	63	1	98.4
12 to 48 months (90 cases).....	87	3	96.6
Average.....			97.4

group of 13 patients who failed to make a favorable response to the use of aluminum hydroxide and later had surgical procedures are included. In other instances the location of the ulcers and the types of problems encountered at the time of the original examinations and the results of the treatment are given in table 1.

*Uncomplicated Duodenal Ulcer.*—The largest number of patients had uncomplicated duodenal ulcer; 154, or two thirds, of the 246 cases were included in this group. The results obtained in terms of duration of complete and continuous remissions are shown in table 2.

Since 97.4 per cent of 154 patients had satisfactory results, this form of therapy should offer a good prognosis in uncomplicated duodenal ulcer if the patient will follow management. Since the patients who had continuous remissions from two to eleven months may be said to have had only a favorable initial response to treatment, we believe that special significance should be given to the group of 87 patients of whom the duration of the continuous remission was known to have existed longer than one year (table 3).

*Complications—Duodenal Ulcer, Massive Hemorrhage.*—Fifteen patients who had massive hemorrhage from duodenal ulcer at the start of treatment have continued to follow management. Twelve patients, or 80 per cent, have obtained satisfactory results. Five

TABLE 3.—*Duration of Continuous Remissions, Uncomplicated Duodenal Ulcer*

	Cases
From 1 to 1½ years.....	25
From 1½ to 2 years.....	19
From 2 to 2½ years.....	19
From 2½ to 3 years.....	10
From 3 to 3½ years.....	4
From 3½ to 4 years.....	10
Total.....	87

patients have been followed for from two to eleven months, and 7 have been followed for from one to four years.

*Complications—Duodenal Ulcer, Pyloric Obstruction.*—Since pyloric obstruction from cicatricial stenosis is a classic indication for surgical treatment, this phase of the subject ordinarily would not be considered in an appraisal of medical management. However, the initial roentgen examination may show the presence of pyloric obstruction without actual fibrosis being present. If the condition has been present for a short time, the cause of the obstruction may be spasm or inflammatory edema and may be relieved by medical management. These

9. Collins, E. N., and Knowlton, R. S.: Review of 141 Consecutive Cases of Massive Hemorrhage from Upper Gastrointestinal Tract, Ohio State M. J. 35: 1175-1180 (Nov.) 1939.

factors were suspected in a group of twenty-one cases at the time of the initial examination. Nineteen patients had relief of the obstruction and 12 have been followed, 7 for from two to eleven months and 5 for from one to three years. Medical management, including the use of aluminum hydroxide, was continued and satisfactory results were maintained in each of the twelve instances. Other measures<sup>10</sup> used during the first seven to ten days of treatment were daily gastric lavage and parenteral fluid therapy, including the intravenous administration of hypertonic (3 per cent) sodium chloride, thiamine hydrochloride and ascorbic acid. Daily urinary chloride determinations were made until the obstruction was relieved. The use of aluminum hydroxide has been found a safe procedure and has not increased the tendency to alkalosis of these patients.

**Gastric Ulcer.**—In a series of 68 cases of gastric ulcer it was known that operation had been performed in 7 and no follow-up studies were available in 24 cases. The remaining 37 patients received only medical management. Satisfactory results were obtained in 33 cases, or 89 per cent, even though surgery had previously been advised in certain instances. Since the duration of follow-up studies was only one year or less in 20 of these cases, the permanent value of this study is questionable in this group. However, we were surprised

TABLE 4.—*Gastric Ulcer, 33 Cases*

Satisfactory results on medical management alone		
Twenty cases were followed for one year or less		
Diagnoses at time of original examination include:		
Cases	Diagnosis	Duration of Follow-Up
3	Without complications.....	14, 14 and 18 months
2	Massive hemorrhage.....	2 and 16 months
4	Pyloric obstruction (temporary)	1, 4, 7 and 11 months
4	Deeply penetrating.....	1, 10, 26 and 41 months

to find that satisfactory results were maintained in certain complicated cases, as quoted in table 4.

**Multiple Ulcers.**—In a series of 18 cases a diagnosis of multiple ulcers was made; that is, one or more ulcers were present in both the duodenum and the stomach. Follow-up studies were made on 11 patients, and 2 had had operations soon after the diagnosis was made, 1 for obstruction and the other for recurrence with continued pain. One patient did not follow management. Six of 8 patients, or 75 per cent, who followed the prescribed medical management had satisfactory results. Two of the 6 patients had massive hemorrhage at the time of the initial examination.

**Marginal Ulcers.**—A diagnosis of marginal or anastomotic ulcer was made in 9 cases. Of this group 7 patients had follow-up studies. At the time of this study no operations have been performed, and 5 patients who followed the prescribed medical management have obtained satisfactory results. Three patients were followed two, eight and thirty-three months respectively; 1 patient had relief from a complicating obstruction and 1 patient with the complication of massive hemorrhage at the time of the original examination had been followed thirty-nine months.

## COMMENT

Obviously, the recorded results cannot be attributed to the use of aluminum hydroxide alone. The hygienic needs of the individual patient were considered first,

and many additional factors, such as the avoidance of undue fatigue, stresses and strains, and the taking of at least one feeding between meals received equal emphasis. Prior to starting treatment most of these patients had had recurrences of symptoms two or three times annually for a number of years, but even in these instances the patient may have a spontaneous remission lasting one or more years. It is also known that patients on whom follow-up studies can be made are usually those who will cooperate on any form of management. Since the likelihood of cooperation on the part of the patient is important, one of the aims of the present study was to find a method of treatment which is adequate and yet sufficiently simple so that cooperation may be expected.

We believe that greater emphasis should be placed on the initial visit of the patient to his family physician. If the management advised at this time is adequate and cooperation on the part of the patient is obtained over a long period of time, complications may be prevented in the future.

Although all schools for treating peptic ulcer emphasize the hygienic needs of the individual, most of them believe that special attention should be given either to the secretory or to the motility factors or to both. In 1929 Crohn<sup>11</sup> demonstrated the advantages of aluminum hydroxide as an antacid in the treatment of peptic ulcer. Recently, although Kirsner and Palmer<sup>2</sup> found that it did not have antacid properties equal to a combination of calcium carbonate and atropine, they state "A rapidly accumulating mass of evidence indicates that aluminum hydroxide has a definite place in the treatment of peptic ulcer." Adams,<sup>12</sup> in a critical evaluation of gastric antacids, believes that it is the most satisfactory antacid thus far employed. He also mentions its influence in the adsorption of such toxins as histamine and the possibility of its removing bacteria from ulcerating surfaces. The Komarovs,<sup>13</sup> working with Pavlov pouch dogs, found that it exercises not only an antacid but also an antipeptic action. Quantities which were not sufficient to react with all the free acid of the gastric juice were sufficient to precipitate considerable proportions of pepsin. Therefore it would seem that the beneficial effect of aluminum hydroxide may be due to several factors and not to its antacid properties alone.

## ABSTRACT OF DISCUSSION

DR. JAMES FLEXNER, New York: The fact that Dr. Collins and his associates were able to control the ulcer symptoms satisfactorily in 88 per cent of 246 patients using aluminum hydroxide as the antacid is of great significance. I would suggest, however, a modification of their routine based on studies which have recently been completed. In collaboration with Mr. Michael Kniazuk at the Merck Institute of Therapeutic Research I have studied the effect of various antacids on dogs with hypersecretion and we have continuously recorded the  $p_n$  change which occurred in the stomachs. In studying aluminum hydroxide suspension (amphojel) 30 cc. was used. This caused a rise in  $p_n$  to a level of 4.5 and this level persisted for from four to six hours. When we did comparable studies *in vitro* we found that a similar dose required 810 cc. of tenth normal hydrochloric acid to bring the level back to the control level at which we started. This is a very important feature in that one can decrease frequent small doses, and this is particularly important at night, when the patient can

11. Crohn, B. B.: Clinical Use of Colloidal Aluminum Hydroxide as a Gastric Antacid, *J. Lab. & Clin. Med.* 14: 610-614 (April) 1929.

12. Adams, W. L.: Critical Evaluation of Gastric Antacids, *Arch. Int. Med.* 63: 1030-1047 (June) 1939.

13. Komarov, S. A., and Komarov, Olga: Precipitability of Pepsin by Colloidal Aluminum Hydroxide, *Am. J. Digest. Dis.* 7: 166-169 (April) 1940.

10. Collins, E. N.: Chronic Dyspepsia: Common Causes and Approach to Treatment, *M. Clin. North America* 22: 417-432 (March) 1938.

be allowed to get more rest. Another important point in the report was the excellent record of the authors in the lack of frequent recurrences. This observation brings to mind the possibility that commonly used insoluble alkaline powders which cause  $pH$  rises in the stomach to levels of 9 or 10 may actually be deleterious. This idea is supported by three arguments. In the first place, natural occurring foods, both cooked and uncooked, have a  $pH$  range from 3 to 7. Second, the most severe type of gastritis often occurs in stomachs that have been operated on. The third argument is that at the Second (Cornell) Division at Bellevue Hospital, where we routinely do a gastroscopy on every patient that is admitted to the clinic, we find a very high percentage of gastritis in these chronically affected patients, and we feel that most of their chronic symptoms are due to gastritis and all of these patients have for many years been on the old Sippy type of regimen. While it is generally agreed that gastric acidity should be buffered in peptic ulcer, there is the possibility that the acidity is a protective factor and it should not be completely carried out of the acid range. The work of Dr. Collins and his associates has clearly demonstrated that the buffering effect of aluminum hydroxide is adequate to keep the patient comfortable and allow healing of the peptic ulcer. Their excellent remission record suggests that much of the chronicity of peptic ulcer may be obviated by the use of this type of buffer therapy.

DR. ARTHUR J. ATKINSON, Chicago: I should like to ask what percentage of the authors' cases were treated by the aluminum drip, which seems quite a bit in vogue, and what they consider to be the indication of the continuous aluminum drip. Physicians in Chicago also have had some good results in using aluminum preparations, but we have had good results using almost any medicament, antacid, sometimes no medicament, in the treatment of the ordinary peptic ulcer. It is in the severe ulcers that result after operative procedures that we have a great deal of trouble. Dr. Ivy, in attempting to evaluate various types of treatment, performed the Mann-Williamson operation on dogs and used aluminum hydroxide in an attempt to prevent and to cure ulcers. The results in these Mann-Williamson dogs were unsatisfactory, and that was probably due to the aluminum hydroxide interfering with phosphorus metabolism, with loss of phosphates. In these dogs the pancreatic juice and the biliary secretion enter the intestine lower than usual, so that the aluminum hydroxide is allowed to form chlorides in the stomach; then aluminum phosphates form with a loss of phosphorus. This may not be of significance in the ordinary ulcer patient, when an ordinary diet has an abundant amount of phosphorus, but in patients having a disturbance of the normal physiology of the stomach due to operative procedure this loss of phosphorus may delay healing. In order to cure and to prevent ulcers in Mann-Williamson dogs, Dr. Ivy used aluminum phosphate to prevent the formation of aluminum phosphate by the aluminum hydroxide. The aluminum phosphate gave better results than anything he had used so far but produced a slight anemia, which was corrected by the administration of iron. I then used the aluminum phosphate in the clinical treatment of ulcer of patients with complicated and some uncomplicated ulcers and found that the aluminum phosphate also was satisfactory. We do not claim that aluminum phosphate will be any better than aluminum hydroxide in the ordinary ulcer excepting in such patients as may have a relative absence or deficiency of secretion of the pancreas or of the bile with a loss of those alkaline intestinal juices.

DR. I. H. EINSEL, Cleveland: My experience with aluminum hydroxide is now over a period of twelve years, and the authors' results have conformed closely to those which my associates and I have obtained. In our series success has been 92 per cent, in the experience of Collins and his co-workers 88, and there is no fundamental difference. How does it act in the cure of peptic ulcer? We have followed cases four years with repeated gastric analysis, and we find that we can determine the level of the free acid in the stomach by the amount of the aluminum hydroxide gel intake. Before starting the patient on aluminum hydroxide gel we do a gastric analysis with the alcoholic test meal. This is repeated frequently to determine whether the dosage of aluminum hydroxide gel is adequate.

If it is not we increase the dosage. After a year or a year and a half we find that the free acid at the height of the stimulating test meal many times goes no higher than 5 units, and a total of no higher than 12. Therefore the secretion of free hydrochloric acid is controlled, and that is the condition we are most interested to have in the gastric juice so that the ulcer is able to heal. Second, we found that the volume of secretion, the stimulation of aluminum hydroxide, is much less than with other antacids. Third, the secretion of mucus is increased in the gastric juice volumetrically determined in these specimens, with the stimulation due to the alcoholic test meal. The cases of failure are of more interest than those of success. Why do we have a failure in the treatment with aluminum hydroxide? We must critically analyze our failures to make sure we are not trying to deal with operative gastrointestinal cases, such as cases with obstruction with organic disease at the pylorus; second, that we do not have perforating duodenal or gastric ulcers into the pancreas or that we are not trying to heal a carcinoma of the stomach. Ulcerative cancer of the stomach under aluminum hydroxide therapy appears to heal, but in a few months the carcinoma overshadows the ulcer syndrome and we are chagrined because of the patient's having appeared very much improved at first but now the real nature of the ulcer becomes apparent to any one. In our failures we should be sure that we are treating really medical gastrointestinal cases and that they are not surgical problems.

DR. ISIDOR GREENWALD, New York: I should like to ask the authors whether they have observed in their series any indications of alkalosis or of a hypovitaminosis. The first question is suggested by the observations made by a previous discussor that aluminum hydroxide diverts phosphates to the bowel. If it does that, and one must take for granted that it does in some cases, it must tend to produce alkalosis. The second question is suggested by the fact that aluminum hydroxide is one of the best agents in the chemical laboratory for the absorption of many chemical substances, many of which can be removed later with only the greatest difficulty. It is rather important to be sure that aluminum hydroxide, given to persons whose diet may not be very rich in one or more vitamins, does not remove or make unavailable to them such vitamins. With the record of gastroenterologists of producing scurvy and beriberi on restricted diets, or the production of alkalosis by the use of bicarbonate, I believe that the use of aluminum hydroxide or other materials of the kind for years should be discouraged. At any rate, it ought to be used with a great deal of caution.

DR. MANFRED KRAEMER, Newark, N. J.: In the wave of enthusiasm for the use of aluminum hydroxide, with or without a drip, a few words expressing its disadvantages are apropos. I have used aluminum hydroxide for a number of years. My initial enthusiasm has weakened because the anticipated results were no better than those usually obtained with the commonly employed antacids. The 88 per cent of remissions is not unusual in any well controlled study by a clinician who is careful in the management of his cases. These results are no better than usually reported in large series employing any antacid. One of the chief disadvantages of aluminum hydroxide is its expense. Expense of treatment is an important factor in ulcer patients. In an industrial community the average income of ulcer patients is probably \$35 a week. They are the heads of families, young men with young children. In order to supply aluminum hydroxide jelly in the amount mentioned by the authors the patient would have to expend about \$3 a week for his aluminum hydroxide. This is too large an item in the budget of the average wage earner. I am sure that an equal effect can be obtained with cheaper antacids. The constipating effect of aluminum hydroxide is a decided disadvantage. A case of intestinal obstruction has been reported. In searching for an ideal antacid we must seek one that does not have such discouraging and disagreeable side effects as this constipating action of aluminum hydroxide, which forces many patients to discontinue its use. We are not certain as to how aluminum hydroxide works. I do not think it works as an antacid. I think the effect obtained by aluminum hydroxide is due to its astringent action on the bowel wall. Aluminum hydroxide does not give a  $pH$  of anywhere near 7, even when used in large amounts. Some of the good

results obtained in the healing of ulcers is due to the astringent action of the aluminum chloride formed; this must have the same astringent effect on the stomach as aluminum acetate preparations on cutaneous ulcers.

DR. E. N. COLLINS, Cleveland: Time will not permit adequate consideration of the many questions raised. Certain questions are answered in the manuscript. In answer to Dr. Greenwald's question, no patient in this series developed any tendency to alkalosis during treatment, which was one of the chief reasons for giving this report on the use of aluminum hydroxide. The question of the interference with the absorption of vitamins has received earnest consideration. We are using a much more liberal diet than we used previous to the use of aluminum hydroxide. Probably the most significant objective evidence which we can present from observations of more than 1,000 cases in which this form of treatment is administered is that the gain in weight per patient for a unit of time has been greater than while using any other antacid. A means of overcoming the mildly constipating effect of using aluminum hydroxide has been presented. The alleged instance of intestinal obstruction has been discussed by Dr. Clement R. Jones Jr. and Drs. V. C. Rowland and E. E. Woldman in communications to the Editor of THE JOURNAL, Dec. 9, 1939. In this instance adequate dilution in the drip method of treatment was not used. Morphine was given every four hours for several days. Many of the patients in this series had symptoms in remittent attacks for twenty years prior to the time treatment was started. Since this presentation was a factual report of results obtained, only certain references to the mechanism of action could be mentioned. Dr. Flexner asked about the use of antispasmodics. We always use antispasmodics during the first two or three weeks of treatment, until the patient becomes adjusted to his new form of living. The drip method was not used in over 10 per cent of the complicated cases, because several years ago we had trouble with several types of apparatus. We believe the physiologic principle back of this form of treatment is sound, and again we are using this method more frequently because of improvements in apparatus.

## THE CUTANEOUS DIAGNOSIS OF GONOCOCCIC INFECTIONS

### A FURTHER REPORT

BUDD C. CORBUS, M.D.

AND

BUDD C. CORBUS JR., M.D.

CHICAGO

A person infected with a specific organism is in a state of hypersensitivity to that organism as long as it remains in the body.

The reaction of the skin to gonococcus toxin in persons infected with the gonococcus is a manifestation of allergy the exact nature of which is not known at present beyond the fact that it is a local tissue response between antigen and antibody. That this reaction denotes clinical specificity may be demonstrated by the passive transfer or Prausnitz-Küstner reaction first demonstrated in gonorrhea by Engel and Vigliani<sup>1</sup> in 1935. In a preliminary report a little later, the senior author also called attention to this proof of clinical specificity.

As early as 1909 Bruck<sup>2</sup> called attention to the fact that persons infected with the gonococcus showed an allergic reaction to the cutaneous application of killed gonococci similar to that shown by tuberculous persons to the Pirquet test. In the preliminary report published in

1936 the senior author<sup>3</sup> pointed out that by heating the standard bouillon filtrate in an autoclave at 15 pounds pressure for fifteen minutes for two periods, with an average temperature of from 115 C. to 120 C., the antitoxin-forming (thermolabile) substance was destroyed. After an extensive trial with the thermostable substance as an antigen we believe that it is inferior to the standard filtrate for eliciting a sharp cutaneous response. This was confirmed by Conrad<sup>4</sup> in 1936 and by Wishengrad<sup>5</sup> in 1939.

This cutaneous manifestation of allergy in specific gonococcic infections has been of considerable worldwide interest, especially the more when one considers that, beginning with Bruck in 1909, there have been throughout the world some forty-six contributors on this subject. Many different types of antigens have been used by the foreign contributors. They comprise whole gonococcus and many different kinds of extracts. The most popular, however, seems to have been a German-made preparation called "compligon," which was supposed to contain gonococcus toxin.

Heidenreich<sup>6</sup> in 1934, using gonargin (a polyvalent gonococcus vaccine) and compligon, reported reactions similar to ours, namely that twenty-four hours following an intracutaneous injection there appeared a central red papule surrounded by a diffuse red areola of the size of a one-mark piece (approximately 24 mm.) to the size of a five-mark piece (approximately 38 mm.). He calls attention to its value as a diagnostic aid in latent gonococcic infection.

In this country the papers of Conrad, Rossett<sup>7</sup> and Wishengrad are of recent date and of considerable interest. With the variance of workers and preparations it follows that a divergence of results occurred. Twelve of the contributing authors doubt the efficacy of this cutaneous test, whereas, on the other hand, nineteen authors not only state that it is of great value but claim that it is specific.

In 1930 Wolfgang Casper<sup>8</sup> stated that, by using a protein-free carbohydrate as an antigen, cutaneous reactions could be elicited in patients with gonorrhea. He further stated that this allergic reaction marked an advance in the diagnosis and prognosis of gonorrhea.

Conrad in 1936 reported a series of 100 cases: fifty negative and fifty positive results. In his "positive" group 98 per cent averaged a reaction measuring 2.32 cm. after forty-eight hours. In the "negative" (control) group 18 per cent revealed an average of 0.2 cm. reaction after forty-eight hours. He believes that coincidental infection neither modifies nor intensifies the cutaneous response in infected patients. He concludes that gonococcus filtrate (Corbus-Ferry) has a definite value as a cutaneous sensitization test for gonorrhea.

With the standard bouillon filtrate as the antigen, Wishengrad of the Central Gonorrhea Clinic in New York believes that there is a definite diagnostic value in the cutaneous test. He states that this procedure should be used primarily as an aid to diagnosis rather than as a diagnostic agent in itself. He further states

3. Corbus, B. C.: A Skin Test for the Diagnosis of Gonococcus Infections. *J. Urol.* 35: 112-125 (Jan.) 1936.

4. Conrad, C. K.: Gonococcus Filtrate (Corbus-Ferry) as a Skin Sensitization Test for Gonorrhea, *New York State J. Med.* 36: 1767-1768 (Nov. 15) 1936.

5. Wishengrad, Michael: Gonococcus Filtrate Test for Gonorrhea, *Urol. & Cutan. Rev.* 43: 386-389 (June) 1939.

6. Heidenreich, Heinz: Die Intrakutanreaktion bei Gonorrhoe und ihre Bedeutung für die Diagnose, *Dermat. Wehnschr.* 99: 1525-1532 (Nov. 24) 1934.

7. Rossett, N. E.: Skin Reactions to Extract Prepared from a Gonococcus Bouillon Filtrate, *Yale J. Biol. & Med.* 11: 345-354 (March) 1939.

8. Casper, Wolfgang: Spezifische Cutireaktionen an Gonorrhöikern mit spezifischen, eiweissfreien Substanzen aus Gonokokken, *Klin. Wehnschr.* 9: 2154-2158 (Nov. 15) 1930.

Read before the Section on Urology at the Ninety-First Annual Session of the American Medical Association, New York, June 12, 1940.

Reproductions of the kiodachromes and additional references to complete the bibliography on the subject are included in the authors' reprints.

1. Engel, Carl, and Vigliani, M. R.: Die Gonorrhoe als Testkrankheit bakteriell-allergischer Vorgänge, *Wien. klin. Wehnschr.* 48: 48-51 (Jan. 11) 1935.

2. Bruck, C.: *Deutsche med. Wehnschr.* 35: 470, 1909.

that in the proper evaluation of this test it is necessary to study a large number of both positive and negative reactions.

It is interesting to note that Rossett in this country during 1939 made use of Casper's suggestion and prepared an antigen derived from the fractional precipitation of the standard bouillon filtrate, which was reduced to a fine brown powder having characteristics of a polysaccharide. Rossett injected his antigen intradermally, using 0.1 cc. of 0.9 per cent saline solution containing 0.2 mg. of the powder. In 60 per cent (six of ten) of his acute cases his reaction consisted of more than 1 cm. of erythema and 0.5 cm. of induration. Similar reactions occurred in 39 per cent (twenty-two of fifty-six) of the chronic cases.

Since the original work on the cutaneous test was begun five years ago the efficacy of a positive reaction has already been established by finding the reaction positive in a large group of gonorrheal infections. The question constantly uppermost in our minds has been: How can the specificity of this test be further demonstrated in regard to its negative phase in order to establish beyond a doubt its efficacy and reliability in the diagnosis of the oft encountered obscure case of gonorrhea? To further this end an additional study was made, the bouillon filtrate being used as an antigen and the broth medium as a control on fifty infected persons as encountered in public dispensary practice, on 100 noninfected students as a control series and on fifteen patients (duration of the disease varying from two months to one and one-half years) in private practice previously cured with the bouillon filtrate.

The additional fifty patients with known infection of two or more weeks' duration showed forty-five, or 90 per cent, positive results. Accurate measurements were taken of the reaction and kodachromes were made. These reactions were tabulated and an average dimension was calculated from the individual measurements. These were characterized by a central indurated area, the diameter of which averaged 1.7 cm., together with a concentric erythema which averaged 4.02 cm. in diameter. This test, as in other intracutaneous diagnostic procedures, should be read forty-eight hours following injection.

In the control series, performed on 100 students with a negative history of gonorrheal infection, 86 per cent gave negative responses. It is important to bear in mind Wishengrad's statement that one must see a large number of both positive and negative results before properly evaluating the two types of reaction. Seventy-five of the eighty-six exhibited merely a minimal central induration, varying from 0.5 to 1.5 cm., with no surrounding erythema. The remaining eleven showed the same central induration, but the induration was surrounded by varying shades of a very faint ghostlike erythema. Fourteen of the known negative cases gave a pseudopositive reaction; i. e., indurated areas without erythema, and erythemas without centrally indurated areas. The basis for these pseudopositive reactions in the control series does not appear entirely clear. It was at first suspected that they were due to an allergic state of the patient himself, which could be elicited in the history in several of the fourteen cases. This, however, was not in accord with the observations of an allergist who tested fifteen patients selected at random in private practice and noted no cutaneous response whatever.

Fifteen patients in our own private practice were encountered, all of whom were treated and "cured"

with bouillon filtrate; 100 per cent of these cases gave the typical negative response.

Finally it is necessary to mention the patients who had been given sulfanilamide previous to their first appearance at the office. It was found that this form of chemotherapy frequently modified the intensity or caused the total disappearance of the expected cutaneous response.

#### SITE OF INJECTION AND METHOD OF INJECTION

Notwithstanding the fact that the majority of cutaneous tests are performed on the flexor surface of the forearm, we prefer to use the extensor surface of the upper arm. The skin is thicker at this point and the intradermal placement of the antigen more easily performed than in the area in which the epidermal layers are less well defined, as on the volar surface of the forearm. It is important to remember that injections of the antigen subcutaneously are of no value whatever.

The standard tuberculin syringe is employed with a special intracutaneous needle, preferably a 25 to 27 gage. The needle is introduced parallel to the surface of the skin, care being taken to advance the needle slowly, with the oblique side upward, penetrating the papillary layer to a depth of somewhat less than a millimeter. We inject 0.1 cc. of the standard filtrate and 0.1 cc. of the broth control—one about 3 inches above the other. When the injection has been correctly placed a wheal appears which is not translucent but white and sharply circumscribed, with a rose-pink border. The needle can usually be seen dimly through the epidermis.

#### EVALUATION OF CUTANEOUS TEST

We believe that the test should be employed primarily as a diagnostic adjunct and not as the sole means of diagnosis. It should always be accompanied by routine measures, such as smear, culture and complement fixation test when indicated. However, as already pointed out by Cumming and Burhans,<sup>9</sup> this intracutaneous (0.1 cc.) injection often causes stimulation of latent gonococcal foci, thus making it possible to obtain positive smears and cultures heretofore not demonstrable in a given case.

In addition we believe that this test may be used as a criterion for cure, because the cases herein presented in which cures were brought about all showed a typical negative response. This occurs because when the person is no longer infected with an organism he ceases to remain hypersensitive to that organism or its antigen. This test as a criterion for cure is not reliable in cases in which intensive chemotherapy has been employed until from three to four weeks after such treatment has been discontinued.

#### SUMMARY AND CONCLUSION

A person infected with a specific organism is in a state of hypersensitivity to that organism as long as it remains within the body.

In a control series of 100 persons known not to be infected with gonococci 85 per cent gave negative reactions to the cutaneous test described.

According to our experience, this test as a diagnostic adjunct in gonococcal infections is more valuable than any other procedure previously available.

636 Church Street, Evanston—55 East Washington Street, Chicago.

9. Cumming, R. E., and Burhans, R. A.: Experiences with the Gonococcus Filtrate (Corbus-Ferry) and Other Forms of Intradermal Therapy in the Treatment of Gonorrhea, *J. A. M. A.* 104: 181-186 (Jan. 19) 1935.



## ABSTRACT OF DISCUSSION

DR. MICHAEL WISHENGRAD, New York: I had no idea that the gonococcus filtrate was being used as a cutaneous test in gonorrhea as extensively as some clinicians have indicated to me in the past few days. I was pleasantly surprised at the fact that the test was not being found too difficult for practical purposes, which I at one time suggested. I also suggested that if one would take the trouble to learn what constitutes a positive and what constitutes a negative reading one would find that this test could be relied on. I agree with the warning that the test should be considered an aid rather than a diagnosis in itself. I have studied more than 500 cases. A negative test may mean as little as a negative Wassermann in the chancre stage. Each requires further checkup. A positive reading should serve more nearly as a probable diagnosis or at least should serve to increase suspicion in a particular case, so that repeated tests would be continued until a more definite diagnosis is made. Cases were diagnosed by smear and culture in several instances only after a positive cutaneous test indicated the need for repetition of these smears and cultures. If we ignore the doubtful readings, as I believe we should, we restrict the field of usefulness of this test only slightly. The acute cases may be negative in the early phases—perhaps in the first two weeks. This is true of the complement fixation test also. If positive (in the acute case) so much the better, but no reliance should be placed on a negative test at this stage. But it must be noted that the diagnosis in even the admittedly more difficult female cases is relatively easy in the acute stage by the usual bacteriologic means. As the proponents of the complement fixation test pointed out, so in the cutaneous test do we suggest greater value in the chronic case. Here we need help most, because of paucity of signs, or because superinfecting nongonococcus organisms becloud the picture. The test can be added to tests for determining cure. In my experience this test became negative before the complement fixation test did and was more reliable. I agree with the authors that sulfanilamide has beclouded the picture somewhat. I prefer not to use it in sulfanilamide cases. Cultures are not yet available to the private practitioner. Even in a big service like the New York City Health Department we don't get half enough.

DR. JOHN H. MORRISSEY, New York: Diagnostic tests for gonorrhea are completely unavailable. From that angle the work of the authors is important, but its inherent weakness lies in the fact that the test is likely to be valueless if sulfanilamide has been administered. We have to choose between an indeterminate test and the indeterminate results of sulfanilamide therapy. Perhaps most of us would prefer to take a chance, if we had to choose, on the sulfanilamide therapy and discard the test. The work of the authors is perhaps one step in that direction, but the well known criterion is the culture, and what is a \$5 culture on these patients if they are going to stay thirty or thirty-five days in the hospital and then go out and reinfect somebody else, as I am sure a great many of them do. There should be some well defined and accepted standardized criterion of cure, possibly determined by the American Urological Association. The value of sulfanilamide therapy is diminished largely by the disarming effect of the drug on the urethral discharge and the other symptoms in the none too intelligent patient, in the type of patient seen in the municipal and charity hospitals, hospital wards and clinics. It has been my experience that perhaps less than 50 per cent of these patients are actually cured and I feel that the remainder are potentially infectious when they are discharged and there has been no further opportunity of checking on them. Attempts at legislative control of the venereal problem are futile, if negative smears merely are depended on as an evidence of cure. Negative cultures should be obtained and should establish cure in every case, regardless of the cost of the procedure, if the problem is to be handled in this way. The contribution of the authors to today's program will aid greatly in the attempt to control the disease at the source, namely in the chronic and cured infectious patients, particularly in permitting

the patient to see that he is still uncured and can still transmit the disease.

DR. BUDD C. CORBUS SR., Chicago: In relation to the test and the use of sulfanilamide therapy, we have seen on several occasions that patients have had large doses of sulfanilamide who also on examination had profuse discharge with gonococci present. The cutaneous test was negative. We all know that the sulfanilamide derivatives impair the hemopoietic system in the body and it would be natural to expect this response. However, I would suggest that, when sulfanilamide therapy has been employed and a cutaneous diagnostic test is contemplated, one should wait from four to six weeks afterward until all the sulfanilamide is out of the patient's body; then one can determine whether the cutaneous test in the patient is positive or negative.

ANEURYSM OF THE VENTRICLE OF  
THE HEART

MARSHALL N. FULTON, M.D.

BOSTON

The prevalence of coronary occlusion and myocardial infarction as a disease entity has led to widespread interest in this condition, its complications and the sequelae. Among the less common end results of infarct of the heart is the formation of ventricular aneurysm. Aneurysm of the ventricle may occur from causes other than infarction, namely from abscess of the heart wall, from trauma, from ulcerative lesions of bacterial endocarditis or from congenital defects. Instances of this type, however, are rare. The majority of ventricular aneurysms arise as a result of infarction following coronary thrombosis. Clinical interest in this problem has received stimulus from the fact that ventricular aneurysm can be diagnosed with accuracy before death and is known to be compatible in some instances with several years of reasonably active life. My purpose in this communication is to review the pathologic, clinical and roentgenologic features of ventricular aneurysm, to report the course of two patients in whom this lesion was recognized during life and to call attention to other conditions, particularly the rare occurrence of a syphilitic lesion, that may be mistaken for aneurysm of the ventricle.

Current interest in this subject is shown by the appearance in the recent literature of several papers dealing with various aspects of ventricular aneurysm.<sup>1</sup> The reader is referred to these for a discussion of historical aspects and references to the earlier literature. It is the roentgenologist who has made possible the accurate recognition of ventricular aneurysm during life. Steel in 1934<sup>2</sup> emphasized the importance of roentgenologic, and particularly of fluoroscopic, examination in establishing the diagnosis. He pointed out that in the early stages bulging of the ventricle may be very slight and that an aneurysm can be present without showing up in the anteroposterior position, thus stressing the necessity of roentgen examination in various degrees of rotation. More recent publications likewise have noted the helpfulness of careful x-ray study in delineating aneurysm and differentiating it from the usual type of cardiac hypertrophy with dilatation.

From the Medical Clinic, Peter Bent Brigham Hospital, and the Department of Medicine, Harvard Medical School.

Read before the Section on Radiology at the Ninety-First Annual Session of the American Medical Association, New York, June 13, 1940.

1. Parkinson, Bedford and Thomson.<sup>4</sup> Ball,<sup>5</sup> Berk.<sup>6</sup>

2. Steel, David: *The Roentgen Diagnosis of Cardiac Aneurysms*, J. A. M. A. 102: 432-436 (Feb. 10) 1934.

## PATHOLOGIC AND CLINICAL MANIFESTATIONS

The steps in the healing process that occur following myocardial infarction have been clearly defined recently by Mallory, White and Salcedo-Salgar.<sup>3</sup> Briefly stated, these consist in the replacement of necrotic muscle by connective tissue, which in turn becomes converted into a firm fibrous scar. The time at which this area "gives way" in the formation of an aneurysmal dilatation has not been clearly determined. Aneurysms of the ventricle have been found at autopsy as early as six weeks after coronary occlusion, though the average time at which they have been discovered clinically is much longer than this, as will be noted later on. The frequency with which aneurysm of the ventricle forms after coronary occlusion, again, is a point difficult to determine definitely. The various series which have been reported<sup>4</sup> indicate that among autopsies either aneurysm or aneurysmal dilatation is found in something like one out of every twelve or fifteen cases in which death does not occur soon after the first occlusion has occurred. It is not, therefore, a particularly rare condition. Its site in the ventricle will depend, obviously, on the location of the infarcted area. Just as the left anterior descending coronary artery is the vessel which most commonly shows complete occlusion, so aneurysms are found most frequently in areas supplied by this vessel, namely at the apex or anterior wall of the left ventricle. They occur much less frequently on the posterior wall and only rarely are they in the right ventricle. They may be of saccular form but more usually exist as a diffuse bulging, varying in diameter from a few centimeters up to a dilatation almost equal in size to the remainder of the ventricle.<sup>5</sup> The wall of the aneurysm commonly measures from 2 to 4 mm. in thickness. Representing as it does a thinned out, healed scar it is composed of dense firm fibrous tissue, occasionally showing a few remaining strands of muscle. There is often a calcium deposit both within the wall of the sac and in the blood clot that fills the aneurysm. Almost always the overlying pericardium is found to be densely adherent to the heart. There may or may not be hypertrophy of the remainder of the heart muscle. Study of the coronary vessels shows complete obstruction of the branch supplying the involved area and varying degrees of sclerosis and atheroma, at times with occlusion, in the other branches.

The diagnosis of ventricular aneurysm is based on three aspects: the clinical history and course, the physical examination and the roentgenologic study. While the last of these is by far the most important, each one may contribute in some measure.

## HISTORY

There is almost always a history pointing to an attack of coronary occlusion at some time in the past. The time interval elapsing between this and the development or recognition of the aneurysm is variable. In the series reported by Parkinson, Bedford and Thomson<sup>4</sup> it differed all the way from three months in one case to seven years in another, the average time being seventeen months. Ball's case<sup>5</sup> was diagnosed as aneurysm of the left ventricle two and a half weeks after a severe attack of pain in the chest, though the patient six weeks

previously had had a sensation of substernal pressure and difficulty in breathing. In two of the cases here reported the aneurysm was recognized in the first instance two years after the first coronary attack, and suspected in the other during the convalescence, the evidence of enlargement having been noted some eight to ten weeks after the occlusion. Obviously this time interval will depend on the accuracy and reliability of the history as well as the frequency and care with which examinations are made. Coronary occlusion not characterized by severe pain or other distinguishing features may be entirely missed in obtaining the patient's antecedent history.

There are two further points in the history that are of suggestive importance. Occasionally, as borne out in my two cases and others reported in the literature, patients with ventricular aneurysm give a story of recurrent prolonged precordial pain following the initial episode. This is not pain of short duration as seen in anginal seizures but distress lasting for hours or days. While it may be indicative merely of further infarction of heart muscle rather than of aneurysm formation, it has been noted commonly in the history of these patients. A second point worthy of mention is that these patients often have failed to observe the generally accepted period of from six to eight weeks of bed rest for convalescence and have resumed activity much sooner than this period after an obvious coronary attack. Whether the strain incident to such early activity has anything to do with causing aneurysm formation is perhaps speculative, though it has been suggested as a possible factor by some writers.<sup>6</sup> The experimental studies of Sutton and Davis<sup>7</sup> lend some weight to this possibility. These workers observed the changes in the heart of five dogs after ligation of the left descending coronary artery. One dog, allowed to rest for six days after operation before exercise was begun on a treadmill, showed subsequently at autopsy a small, well contracted scar without thinning of the ventricular wall. Four other dogs that were made to exercise within three days after operation were later killed and found to have thin ventricular scars with aneurysmal bulging.

The features in the history, then, of a previous attack of coronary thrombosis, of shortened convalescence following such attacks and of repeated episodes of prolonged pain are those which may lead one in a given case to suspect the possibility of ventricular aneurysm.

## PHYSICAL EXAMINATION

Every one is cognizant of the bizarre precordial pulsations that may be found with any markedly enlarged heart. These are often very misleading and may cause one quite erroneously to suspect aneurysm. There are two unusual types of pulsation that can be of help in support of a clinical diagnosis. The first is a forceful, abrupt, localized thrust, often felt at the apex and caused, presumably, by the outward expanding pulsation of the ventricular bulge. Such an impulse was noted in case 1 of this article and was the first manifestation that led to the suspicion of aneurysm. The other type is a conspicuous, sometimes localized, pulsation felt medial either to the apex beat or to the outer border of cardiac dulness. This feature was notable in Ball's case.<sup>5</sup> It is important to note that, in contrast to this,

3. Mallory, G. K.; White, P. D., and Salcedo-Salgar, Jorge: The Speed of Healing of Myocardial Infarction: A Study of the Pathologic Anatomy in Seventy-Two Cases, *Am. Heart J.* 18: 647-671 (Dec.) 1939.  
4. Parkinson, John; Bedford, D. E., and Thomson, W. A. R.: Cardiac Aneurysm, *Quart. J. Med.* 7: 455-478 (July) 1938.  
5. Ball, David: Aneurysm of the Heart, *Am. Heart J.* 16: 203-218 (Aug.) 1938.

6. Berk, L. H.: Cardiac Aneurysm, *Am. Heart J.* 17: 569-580 (May) 1939.

7. Sutton, D. C., and Davis, M. D.: Effects of Exercise on Experimental Cardiac Infarction, *Arch. Int. Med.* 48: 1118-1125 (Dec.) 1931.

pulsations in some cases of aneurysm may be surprisingly slight, on physical examination as well as fluoroscopically. The heart sounds, as a rule, are muffled and diminished out of all proportion to the force of the cardiac impulse. Gallop rhythm is frequently to be heard. There is nothing distinctive about murmurs—they may or may not be present. The blood pressure, while occasionally elevated, is commonly normal or low. In the series of cases reported by Parkinson and his associates<sup>4</sup> the average reading was 130 systolic, 75 diastolic.

Electrocardiograms are of importance only as they may add to the evidence of myocardial infarction and assist in localizing the lesion in the anterior or posterior part of the ventricle.

#### ROENTGENOLOGIC FEATURES

The greatest help in the examination comes from careful roentgenologic study. It is the x-ray examination more than anything else that has taken ventricular aneurysm from the sphere of pathologic curiosities and made it a recognizable condition of clinical interest. In ventricular aneurysm one usually sees by x-ray



Fig. 1 (case 1).—Postero-anterior view Nov. 14, 1938. Note cardiac enlargement and tortuous aorta. Evidence of aneurysm is lacking in this view, though the left ventricular contour is straighter than usual.

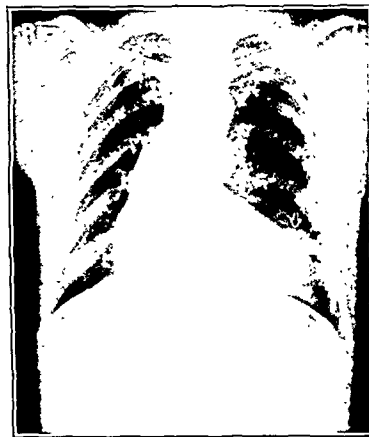


Fig. 2 (case 1).—Appearance May 16, 1939. Note increase in cardiac enlargement and bulge at apex (outlined by arrows) which showed marked outward expansion during systole.



Fig. 3 (case 1).—Appearance Jan. 18, 1940. Note marked increase in size of aneurysm at apex.

examination not only cardiac enlargement, which is nearly always present, but an abnormal contour of the heart, commonly with sharply defined ledging of the ventricular border. The aneurysm appears as a bulge rather than as a hump on the surface of the ventricle. It is generally of the same density as the cardiac silhouette, though in some instances it is conspicuously lighter (fig. 5). This bulge may be missed if the patient is viewed only in the anteroposterior position, and careful study by fluoroscopy, especially in the oblique position, may reveal what is in no wise evident in the routine heart film. By fluoroscopy also one may get important information regarding pulsations. Localized aneurysms may show a paradoxical type of pulsation, expanding outwardly as the ventricle contracts. This feature of the fluoroscopic examination is particularly important to look for. While it is not pathognomonic of aneurysm as distinct from all other lesions (case 3) it indicates a weakened area in the ventricle. Such a paradoxical movement may be recorded in some instances by kymogram, but this affords help only as a permanent record of what can

be seen much more satisfactorily by the fluoroscope. In contrast to this type of localized pulsation, a greatly diminished or feeble beat may be observed in larger aneurysms or those filled with a blood clot. In such instances the unusual contour of the heart produced by the bulge of the ventricular wall is much more to be relied on than the pulsation. As pointed out by Steel,<sup>2</sup> if conditions are such that bulging of the thin walled ventricle is very slight there may be insufficient abnormality in the cardiac silhouette to lead to recognition of the lesion by x-ray examination. Again, apical aneurysms may be difficult to visualize because the bulge may be obscured by the shadow of the diaphragm. Calcification within the wall of the aneurysm or in the clot which it contains may be of aid in diagnosis.

#### LIFE HISTORY

The patient with this condition has an extremely variable course, just as is true in any instance of coronary artery obstruction. His life is hazardous, subject always to further coronary attacks, to anginal seizures or to the development of congestive failure. Some patients, however, do surprisingly well and may

live and remain ambulatory for a period of several years. In Parkinson's series of fifteen patients the length of life for the group averaged about two years after the first attack of coronary thrombosis. This average, among the patients who died, was made up from extremes varying between nine months and five years. One of his patients was still alive and doing fairly well after an interval of seven years. It is a point of considerable interest that these individuals rarely die as a result of rupture of the aneurysm. While this occasionally occurs, rupture is much less common as a cause of death than is gradually increasing cardiac failure or cerebral embolism from a dislodged fragment of clot. The occurrence of rupture of the heart wall following coronary occlusion is much more likely to take place during the first two weeks when necrosis and softening of the heart muscle are most marked.<sup>5</sup>

#### REPORT OF CASES

Within the course of six months, two patients with ventricular aneurysm were observed in the wards of

8. Fulton, M. N.: Acute Hemopericardium: Its Causes and Clinical Manifestations. *M. Clin. North America*, September 1940. Mallory, White and Salcedo-Salgar.<sup>2</sup>

the Peter Bent Brigham Hospital. Each one of these illustrates some of the features of this condition that have been noted.

**CASE 1.**—J. L., a Russian born tailor aged 56, was admitted in November 1938 because of an acute gastrointestinal upset which had come on following the excitement and indulgence incident to his son's wedding festivities. We subsequently learned from the records of another hospital in Boston the following interesting details of his story: In 1935 he began having attacks of angina pectoris. At that time he had slight cardiac enlargement and a blood pressure varying between 180 and 210 systolic. He was able to continue irregularly at his work until December 1936, when an episode of prolonged severe substernal pain occurred. This led to his admission to a hospital, where the clinical examination left no doubt about the diagnosis of coronary thrombosis. It was noted at that time that the heart was slightly enlarged, but it showed no particular abnormality of the beat as determined by palpation. The sounds were described as being of very poor quality. He stayed in the hospital for six months owing to the fact that he consistently had an elevated pulse rate, occasionally a slight fever and recurring attacks of precordial pain and finally because of the occurrence of paroxysmal dyspnea and other signs of congestive heart failure. During the greater part of this period of six months his prognosis was looked on as being very poor. This was early in 1937. He was discharged in June and continued

apex of the left ventricle coming to light approximately two years after his first attack of coronary occlusion but probably being present for a good many months. The unusual pulsation which he had is not an uncommon finding in cardiac aneurysm as just noted and was the feature here which first suggested the diagnosis. He was discharged after a few days but has been seen at frequent intervals since.

In May 1939 an x-ray film (fig. 2) showed greater enlargement of the heart and the bulge of the aneurysm could be plainly seen. At the present time his activity is limited, but he is ambulatory and able to walk several blocks if he does not hurry. Exertion brings on considerable breathlessness, but he is relatively free from angina. A repeat x-ray examination made in January 1940 (fig. 3) showed a definite increase in the size of the rounded prominence at the apex of the left ventricle. This area still shows a marked systolic expansion while the adjacent ventricle is in contraction. No calcification is seen in the aneurysm. The blood pressure is 160/100. The lungs have remained clear and no pitting edema has developed. Physical examination of the heart still shows the extraordinary forceful impulse in the apex area and a to and fro murmur at the base. He takes a maintenance dose of digitalis each day and theobromine three days out of seven.

This case illustrates the classic type of apical aneurysm. It has now been three and a half years since

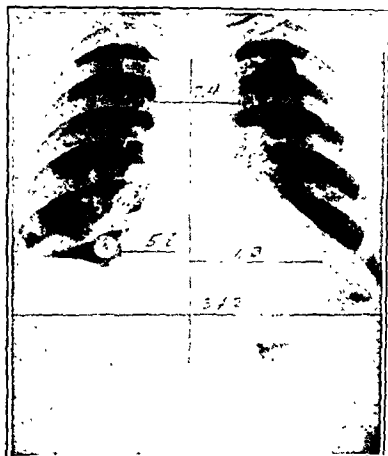


Fig. 4 (case 2).—Appearance July 7, 1938, showing cardiac enlargement but no evidence of aneurysm which arose from posterior wall of the heart.



Fig. 5 (case 2).—Left anterior oblique view taken July 7, same time as the view shown in figure 4, showing bulge (outlined by arrows) projecting from the posterior surface of the heart and exhibiting fluoroscopically a feeble pulsation.

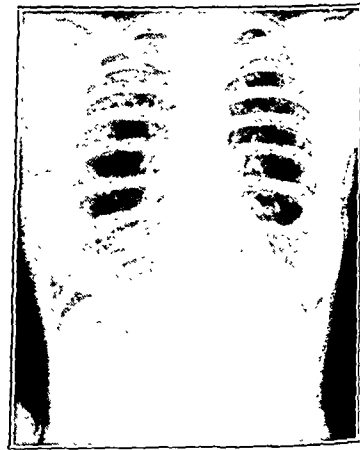


Fig. 6 (case 3).—Appearance Nov. 2, 1937, showing normal heart shadow fourteen months before cardiac pain began. This film was taken to rule out pulmonary tuberculosis.

his convalescence at home, though its course there was interrupted by episodes of severe paroxysmal dyspnea. By June 1938 he was able to walk a half mile or so without ill effect unless he hurried. Much effort was likely to bring on substernal pain and dyspnea.

When he was first seen by us two years after his coronary thrombosis, we could not help but be impressed by the extraordinary impulse palpable in the apex region of the heart. It was a forceful thrust of a most unusual kind—as though a part of the heart were forced out between his ribs with each beat. It was most marked in the fourth left interspace directly above the nipple. The patient said that he had noticed this beating even through his coat for a period of several months. There were systolic and diastolic murmurs over the heart but no objective signs at the time of congestive failure. The blood pressure varied between 170/120 and 135/85 mm. of mercury; venous pressure in the arms measured 95 mm. of water; the vital capacity was 2,300 cc.; the Wassermann and Hinton reactions were negative. An x-ray film showed the heart contour seen in figure 1. By fluoroscopy one could see an outward systolic pulsation near the apex of the heart corresponding to the abrupt pulsation of the chest wall. Electrocardiograms showed curves consistent with an anterior infarction. We felt that the patient had an aneurysm of the

the coronary occlusion occurred. The aneurysm was first recognized by physical examination eighteen months ago, two years after the occurrence of coronary occlusion.

**CASE 2.**—R. S., a business executive aged 55, was seen at the Peter Bent Brigham Hospital in May 1938. Dr. Frank T. Fulton of Providence, R. I., and Dr. Samuel A. Levine of Boston furnished the following notes concerning his antecedent history over a ten year period: He was first seen in 1928 because of mental depression. At this time there was no cardiovascular abnormality. Five years later he had an attack of substernal pain for which his local physician put him to bed. The pain was in the upper part of the chest, radiated to the arms and was associated with sweating and marked prostration. He stayed in bed for only four or five days, insisting on resuming activity earlier than was advised. Six weeks later he had another attack of severe substernal pain, following which he fainted and was subsequently in collapse. At this time the heart exhibited no precordial impulse that could be seen or felt. It did not seem enlarged and had a regular action with a rate of 90, and there were no murmurs. The blood pressure was 115/70; there were rales at both lung bases. The diagnosis seemed clearly to be coronary occlusion, and this was confirmed

by an electrocardiogram. Following this the patient remained at bed rest for eight weeks.

It was during this convalescence that a very considerable increase was noted in the heart size. Whereas at the time of the first attack of pain there had been no demonstrable cardiac enlargement, two months later the heart was definitely enlarged and the whole left side of the chest moved with each beat. There were no murmurs, and the heart sounds were clear and of fairly good character. Because of the marked increase in the size of the heart it was believed that dilatation of the ventricle and thinning of the wall had occurred and the possibility of rupture was feared. The patient made a satisfactory convalescence, however, and was able to return to his work in the summer of 1933, to walk as much as a half mile without disturbing breathlessness or pain and during the following year to be at his office each day from 9 to 6 o'clock. It was noted repeatedly during that year that the precordial pulsation was diffuse, lifting the chest wall with each impulse. Two years later (1935) he had a return of precordial pain and at one time paroxysmal tachycardia shown by electrocardiograms to be of auricular origin. In May 1937 the cardiac impulse was described as neither vigorous nor violent but palpable over an area some 5 to 6 cm. in diameter, lifting the chest wall with each beat. At this time the first opportunity occurred for fluoroscopic study. The heart, as was evident on physical examination, was considerably enlarged. In the left anterior oblique position a large bulge could be seen about the size of

The patient lived until August 1938, which was five and a half years after his first coronary attack. During the last year of his life he had recurrent anginal seizures and occasional attacks of paroxysmal dyspnea. It is of interest that his pain often would come on when he was sitting down and would disappear when he stood up. He noticed this so regularly that he took to doing his work at the office standing at a drawing board. His death occurred presumably from congestive heart failure, following the development of more frequent and severe attacks of paroxysmal dyspnea. Unfortunately there was no postmortem examination.

This case illustrates several of the features of cardiac aneurysm noted: (1) the history of repeated attacks of pain occurring in this instance with a short convalescence following the first coronary attack; (2) the type of aneurysm arising from the posterior wall of the left ventricle definitely recognizable only by x-ray examination; (3) the duration of life for five years from the time when it seems extremely likely that the aneurysm first formed.

#### DIFFERENTIAL DIAGNOSIS

A detailed account of differential diagnosis of cardiac aneurysm would include a number of conditions such as an enlarged pulmonary conus, a syphilitic aneurysm

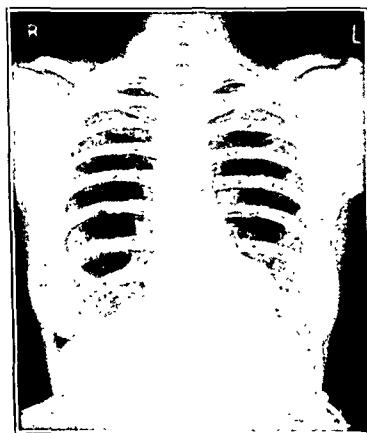


Fig. 7 (case 3).—Appearance March 19, 1939. Note rounded hump on left ventricular border of normal sized heart. This showed a marked expansile pulsation during systole.

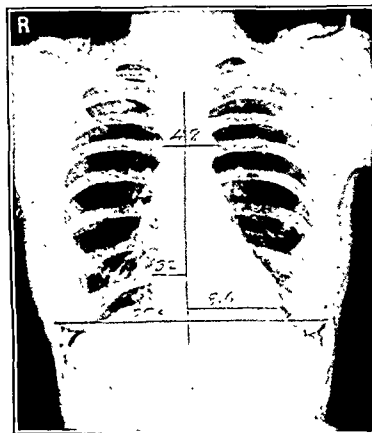


Fig. 8 (case 3).—Appearance May 25, 1939, six weeks after antisyphilitic treatment was started. The diminution in the size of the ventricular bulge may be due in part to exposure of the film during diastole.



Fig. 9 (case 3).—Right anterior oblique view May 25, same time as view shown in figure 8, showing the hump on the left ventricular border.

an orange projecting from the posterior surface of the left ventricle. This bulge was continuous with the heart shadow but appeared distinctly less dense. Cardiac pulsations could be visualized but poorly throughout.

The interpretation of these manifestations was that the patient had a large aneurysm of the left ventricle extending posteriorly. In the absence of any recent change in his progress or physical examination, it seemed quite probable that the aneurysm had been present for several years, very likely having formed soon after the first attack of coronary thrombosis four years before and explaining the unusual impulse which had been noted over his heart then and during the intervening years. It is interesting that at this time (1937), as had been true since his first acute attack, his blood pressure was low, 100/70. There were no murmurs and the lungs were free from rales. Examination at the Peter Bent Brigham Hospital confirmed these observations and x-ray films (figs. 4 and 5) showed the enlarged cardiac silhouette and the unusual prominence which had been noticed by fluoroscopy extending backward from the posterior surface of the heart. (The lack of evidence of aneurysm here in the anteroposterior view emphasizes the great importance of looking for this lesion fluoroscopically with the patient in different degrees of rotation.) Electrocardiograms showed changes in the T waves, most marked in leads 2 and 3, pointing to a posterior infarction.

of the descending aorta or loculated pericardial effusions or cysts. Many instances of cardiac hypertrophy and dilatation, particularly those seen following coronary occlusion, may present features suggestive of aneurysm. There is one condition which, though rare, simulates aneurysm of the heart and may be so misdiagnosed, namely the occurrence of a localized syphilitic lesion of the heart wall. It is important to differentiate this condition because antisyphilitic therapy may lead to great improvement. An illustration of such a lesion is offered by the following unusual case recently observed at the Peter Bent Brigham Hospital:\*

CASE 3.—M. A., a housewife aged 41, complained in March 1939 of easy fatigue, vomiting and pain over her heart, all of which she had noted for about two months. A year and a half before she had been seen by her physician because of weakness. An x-ray film of the chest taken at that time to rule out tuberculosis (fig. 6) revealed a heart of normal size and contour and no abnormality in the lungs. The pain of which she now complained had come on following a mild respiratory infection

\* Dr. Rowland Parris of Falmouth, Mass., and Dr. Julius G. Kelley of Pocasset, Mass., furnished notes on this patient and some of the x-ray films shown in figures 6 to 11.

with cough. She described it as a dull, continuous ache over the entire precordial area, radiating to the left shoulder and down the left arm, intensified at times—both when she was quiet and when she was exerting herself or moving about—by a sharp, stabbing sensation of the same distribution. It had never been of the severe agonizing type seen in coronary

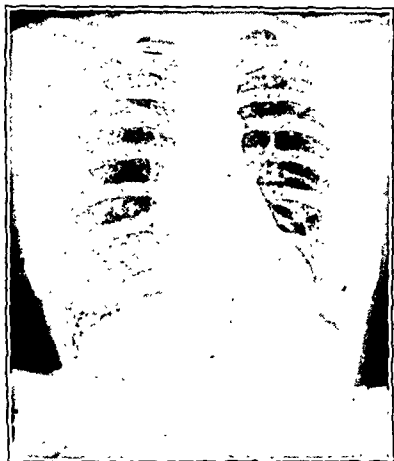


Fig. 10 (case 3).—Appearance April 1, 1940, thirteen months after antisymphilitic therapy was started. Compare with figure 6. The heart is slightly larger but the contour is practically normal.

precordium and extending upward into the upper left thorax. The heart seemed normal in size and was slow and regular and without murmurs. The blood pressure was 100/70. The nature of her trouble was entirely obscure until roentgen examination of the chest showed the unusual appearance of the heart shadow as seen in figure 7. This disclosed a remarkable rounded hump on the left ventricular border of an essentially normal sized heart. By fluoroscopy this hump could be seen to have an extraordinarily expansile pulsation, bulging outwardly to an extreme degree with each contraction of the ventricle. The fluoroscopist expressed concern that the lesion might rupture at any moment. This finding ruled out the possibility of a solid tumor and led to the presumptive



Fig. 11 (case 3).—Appearance April 1, 1940, same time as view shown in figure 10. Note persistence of small hump at site of original lesion. This still shows outward expansion fluoroscopically during systole.

A second Wassermann test confirmed this finding. The subsequent course points strongly to the diagnosis of a localizing syphilitic lesion of the heart wall. The patient was started immediately on potassium iodide and injections of bismuth. Within three days the elevated temperature that she had been having dropped dramatically to normal and within the month that she remained in the hospital her precordial pain gradually and entirely disappeared. She

occlusion but had been such as to incapacitate her and keep her awake at night. She had also noted that relatively little effort made her distinctly short of breath. She had observed no edema and had been able to lie flat in bed without any difficulty in breathing. She also complained of gaseous eructations and vomiting of gradually increasing frequency. There had been a loss of about 20 pounds (9 Kg.) during the past year.

The unusual feature on physical examination was a diffuse impulse felt all over the upper left thorax. The diagnosis of the common type of ventricular aneurysm was (1) the absence of any history pointing to coronary occlusion, (2) the continuous, persistent pain of two months' duration and (3) the x-ray finding of a fairly sharp, localized hump rather than a bulge, and that on the border of a normal sized heart. The likely possibility of a syphilitic lesion was not suspected until a routine Wassermann test was reported as strongly positive.

A second Wassermann test confirmed this finding. The subsequent course points strongly to the diagnosis of a localizing syphilitic lesion of the heart wall. The patient was started immediately on potassium iodide and injections of bismuth. Within three days the elevated temperature that she had been having dropped dramatically to normal and within the month that she remained in the hospital her precordial pain gradually and entirely disappeared. She

was seen again a month after discharge. There had been no return of her pain, and examination showed scarcely any palpable impulse over the precordium. By x-ray examination (fig. 8) the lesion appeared smaller in the anteroposterior view, though still quite prominent in the oblique position (fig. 9). It still exhibited on fluoroscopy a clearcut expansile pulsation with each systole. Following discharge from the hospital the patient was given antisymphilitic arsenicals, and these were continued until December 1939. Subsequently she has received more injections of a bismuth compound. We were informed by her doctors that the pain which she had in her chest and the dyspnea had not returned. An x-ray film taken April 1, 1940, showed almost complete disappearance of the bulge on the ventricular wall (fig. 10), though in the oblique view (fig. 11) there is still evident a slight prominence at the site of the original lesion. Fluoroscopically, one can still detect a paradoxical pulsation in this area, with outward thrust during systole, though this is greatly diminished in excursion from that observed originally.

Figure 12 shows the electrocardiograms taken during the first three months of observation and recently. The inverted T wave in lead 1, which became diminished in depth during the first two months of treatment, is now upright. There is a comparable diminution in the excursion of the inverted T wave in lead 4.

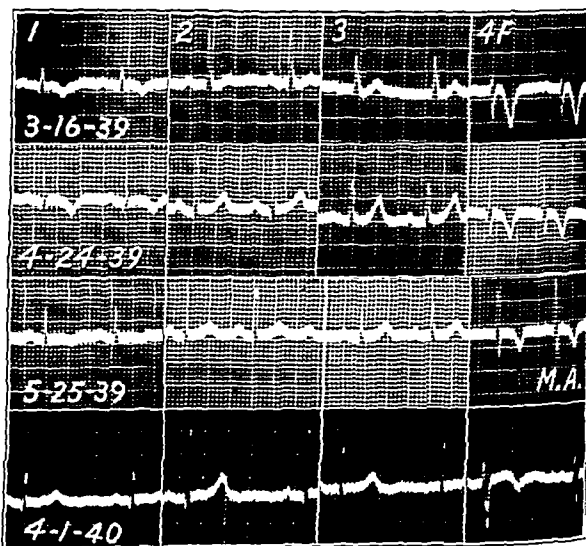


Fig. 12 (case 3).—Standard and precordial leads taken at various intervals. Note change in  $T_1$  from inverted to upright direction, and diminution in the excursion of inverted  $T_4$ .

#### SUMMARY

Aneurysm of the ventricle of the heart occurs occasionally as a sequel to myocardial infarction. While the diagnosis may be suspected in patients who have had coronary occlusion and who present unusual precordial pulsations, it depends in the main on the changes seen on roentgenologic examination. The features here are (1) cardiac enlargement plus a silhouette of abnormal contour with a bulging or ledging of the ventricular border; (2) at times decreased density of the aneurysmal shadow compared to the rest of the heart; (3) either a paradoxical pulsation with outward expansion of the aneurysm during systole or a diminished feeble beat in the aneurysm compared to that seen in other parts of the ventricle; (4) calcification within the wall of the aneurysm or in the clot which it contains.

Patients may live for several years with ventricular aneurysm and enjoy a life of reasonable though limited activity. They rarely die as a result of rupture of the heart.



Three cases are reported: One patient with an apical aneurysm is still alive eighteen months after the lesion was first recognized; one patient with a large posterior aneurysm lived five years after the probable time of its formation, and one patient with a localized syphilitic lesion of the ventricle had a mistaken diagnosis of aneurysm and has greatly improved with antisiphilitic therapy.<sup>10</sup>

1101 Beacon Street.

#### ABSTRACT OF DISCUSSION

DR. WILLIAM J. KERR, San Francisco: Over a period of many years I have had the opportunity to see a number of patients who present some of these features. The changes, first in the fluoroscopic examination of the patient and sometimes in films, are striking and should make one suspect that one is dealing with a bulging of the ventricular wall due to aneurysm. Too often it has been put down as a dilatation of the ventricular wall associated with long-standing hypertension and hypertrophy which preceded the dilatation, as all have seen at autopsy the thinning of the ventricular wall with flattening of the columnae carnae and papillary muscles. One should not wait for the pathologist to make this diagnosis, because Dr. Fulton has pointed out the criteria on which this condition should be suspected and in the more advanced cases the features by which it should be diagnosed. I have been very much impressed by the abnormality of the pulsations seen in such cases. They may be very marked, they may be expanding in the region of the apex of the heart, or they may be the so-called paradoxical type of pulse. In some of the patients I have seen over the years, when the aneurysm is suitably situated there may be a pulsation well inside the left border of what seems to be the cardiac dulness where the aneurysmal sac apparently did not bulge out during systole but where the contracting or active muscle came up against the chest wall well inside the left border. This characteristic should make one suspect this condition, which could differentiate from pericardial effusion on the quality of sounds, and so on. As Dr. Fulton has pointed out, however, the x-ray examination is most helpful in establishing the diagnosis. I suspect from my own experience, which Dr. Fulton may wish to discuss in more detail, that this aneurysm arises rather early in the course of coronary occlusion, that perhaps it arises in the first two or three or four weeks or begins at that stage, and with progressive attacks of coronary occlusion or extension of the process this condition probably becomes more marked. If the aneurysmal sac is next to the diaphragm or against structures where adhesions and fibrosis will be marked, there is not much likelihood of its being progressive unless the coronary occlusion is repeated time and again. My first impression was that this was probably a gummatous process which was bulging outside as well as inside the chamber of the heart at that early stage. However, the subsequent films indicate that there is some bulging, but it is quite likely that it was an extensive gummatous process there which is seen occasionally in the heart of the untreated syphilitic patient at autopsy.

DR. EMANUEL LIBMAN, New York: The frequency of aneurysm of the left ventricle is greater than has been believed. Dr. Kerr has brought up the question How soon can an aneurysm develop? The necrosis occurs and then healing, and in the course of time the involved part is bulged out. But the aneurysm may develop because of the necrosis itself before there is any real fibrosis. With Dr. Benjamin Sachs I have put on record one case in which an aneurysm developed within eleven days after occlusion, there being present an extensive area of necrosis reaching the pericardium. In 1912 I pointed out that not infrequently the diagnosis can be made by feeling a pulsation between the apex and the sternum, the pulsation at the apex being slightly or not at all palpable and a poor first apical

heart sound being present. It is risky to employ this method if the first sound is good. An aneurysm may be present in association with a readily heard first apical sound, but under such conditions I advise against drawing conclusions. I will cite a case in which the diagnosis was based on this method alone: A patient suffering from a ureteral calculus was sent to me for an opinion concerning operative intervention. On palpating the cardiac area I found an aneurysm. I advised against removal of the calculus. The electrocardiogram showed only slight changes. That was in 1934. Cardiac symptoms were not present and there was no history of any. The diagnosis was not accepted and no special care was given to the patient. In 1936 edema of the legs developed, later a systolic murmur, and the aneurysmal pulsation covered a large area. The patient died in 1938 after repeated attacks of heart failure and the development of definite electrocardiographic changes. Some years ago the late Dr. Hermann Mond, at my suggestion, made fluoroscopic studies in a large number of cases. He found three signs that could be present: (1) weak movement of the whole border of the left ventricle, (2) a seesaw motion, the aneurysmal part being bulged out, the rest of the border being drawn in, and (3) an absence of pulsation of part of the border. This last sign was found to be the best evidence of the presence of an aneurysm. It was present in Dr. Fulton's cases. There are at least two conditions in which fluoroscopy or, still better, roentgenkymography is very important. A number of patients who appear to be suffering from a first attack of occlusion have already had one or more previous attacks, latent or unrecognized. There is, of course, a difference in the prognosis and in the length of time for bed rest. Roentgenkymography can aid by revealing an aneurysm, which points to an early infarction. A patient may suffer an occlusion, with electrocardiographic evidence, and later changes may disappear.

DR. SIMON DACK, New York: The fluoroscopic examination is of value not only in the diagnosis of cardiac aneurysm following coronary occlusion but also in the diagnosis of cardiac infarction even when there is no evidence of enlargement or bulging of the left ventricular contour. Dr. Fulton has described the abnormalities in pulsations in ventricular aneurysms. These are (1) an expansile or paradoxical movement of the left ventricular contour and (2) a marked diminution in amplitude of pulsation. These abnormalities in pulsation may be observed also in cardiac infarction even in the absence of a localized bulge. Thus in several hundred cases of cardiac infarction following coronary occlusion studied at the Mount Sinai Hospital, many of which were checked by roentgenkymography, it was found that at least one half showed a systolic expansion or a paradoxical movement of the left ventricular contour, and about one fourth showed a very marked diminution of pulsation. In other words, the area of infarction behaves functionally as an aneurysm. The value of fluoroscopy lies in the fact that the x-ray film may show a heart of normal size and contour without any evidence of localized dilatation. Furthermore, the electrocardiogram following recovery from the attack of coronary occlusion may no longer be typical of infarction or may even return to normal. Observation of the ventricular pulsations in such cases may often be diagnostic.

DR. MARSHALL N. FULTON, Boston: Dr. Kerr has raised the question which Dr. Libman has also touched on as to the most likely time in which the aneurysm may form following coronary thrombosis. Some light has been shed on this question by the recent studies published in the *American Heart Journal* by Drs. Mallory, White and Salcedo-Salgar, who made careful microscopic studies of the heart muscle following coronary occlusion, finding that evidence of necrosis may be detected as early as six hours following coronary obstruction and that the maximum period of necrosis in the heart muscle will be found from four to six days following occlusion. That means that the time in which weakening of the heart muscle is most marked is during the first two weeks. It is known that in this two weeks period the majority of instances of rupture of the heart following coronary occlusion occur. As Dr. Libman pointed out, cases have been recognized of ven-

<sup>10</sup> Since the submission of my paper, an excellent review of the subject of aneurysm of the heart has been published (Dressler, Wilhelm, and Pfeiffer, Robert: Cardiac Aneurysm: Report of Ten Cases, *Ann. Int. Med.* 14: 100-121 [July] 1940).

tricular aneurysm during the first two weeks following coronary occlusion, and other cases have been observed over a period of a month or two months. The average length of time in the series that has been reported is a longer period than that. As stated, it will depend on the frequency of examination and the accuracy of the history that the patient gives. I think it is important to emphasize that when the aneurysm involves the portion of the ventricle buried in the diaphragmatic shadow there may be no demonstrable bulging in the x-ray film. Dr. Steel of Cleveland pointed this out clearly in a paper published in *THE JOURNAL* some years ago. My experience with kymographic study has been that it affords a permanent record of what can be seen on fluoroscopy, but, as far as ventricular aneurysms go, it has not contributed more than that.

## PRIMARY EPITHELIOMA OF THE URETER

EDWARD N. COOK, M.D.

AND

VIRGIL S. COUNSELLER, M.D.

ROCHESTER, MINN.

Carcinoma at any situation in the urinary tract is most serious, and the question of cure is controlled largely by the same factors which govern the cure of cancer in any other organ; namely, early diagnosis and radical treatment by surgery, radium and roentgen rays. Furthermore, the chance of cure is greater if the lesion originates in any portion of the urinary tract that can be completely removed surgically, together with all associated lymphatic vessels. Radical procedures instituted to eradicate any malignant process are always more favorable in the early small lesion of slow growth and are less favorable as the lesion extends and also if it is of greater activity.

Our experience in eighteen positively proved cases of this disease has served to emphasize certain points in diagnosis and surgical management which we have noted are extremely essential if a higher percentage of cures are to be effected than has been the case in the past.

In 1842 Rayer<sup>1</sup> reported the first case of primary carcinoma of the ureter. In 1878 Wising and Blix<sup>2</sup> found the condition at necropsy and noted metastases to the colon, mesentery, peritoneum and liver. Albarran<sup>3</sup> in 1902 mentioned a case in which what he called "papilloma of the ureter" had been diagnosed preoperatively and confirmed by operation, by his master, Le Dentu, and himself in 1899. Since that time reports of cases have occurred sporadically in the literature, and Aschner,<sup>4</sup> followed by Rousselot and Lamou<sup>5</sup> and later by Mackenzie and Ratner,<sup>6</sup> have collected these in a group. Mackenzie and Ratner reported sixty-two cases in 1932. Since that time various cases have appeared in the literature and we add eighteen more seen at the Mayo Clinic during the past nineteen years.

From the Section on Urology (Dr. Cook) and the Division of Surgery (Dr. Counsellor), the Mayo Clinic.

Read before the Section on Urology at the Ninety-First Annual Session of the American Medical Association, New York, June 13, 1940.

1. Rayer, P., cited by Rousselot and Lamou.<sup>5</sup>

2. Wising, P. J., and Blix, C.: *Cancer of Ureters and Secondarily of Mesentery*, *Hygiea* 40: 468-476, 1878.

3. Albarran, M. J.: *Adénome de l'uretère; extirpation; guérison*, *Bull. et mém. Soc. d. chirurgiens de Paris* 28: 838-844 (July) 1902.

4. Aschner, P. W.: *Primary Tumors of the Ureter*, *Surg., Gynec. & Obst.* 35: 749-758 (Dec.) 1922.

5. Rousselot, L. M., and Lamou, J. D.: *Primary Carcinoma of the Ureter: Report of a Case and a Review of the Literature*, *Surg., Gynec. & Obst.* 50: 17-28 (Jan.) 1930.

6. Mackenzie, D. W., and Ratner, Max: *Metastatic Growths of the Ureter: A Brief Review of the Literature and a Report of Three Cases*, *Brit. J. Urol.* 4: 27-35 (March) 1932.

## ETIOLOGIC CONSIDERATIONS

The incidence of this disease is no doubt more frequent than the reports in the literature would indicate. Before the advent of urography and particularly excretory urography, many instances of epithelioma of the ureter went undiagnosed. Since more nearly exact methods of diagnosis have been used, there has been a relatively much greater number of such cases reported during the past ten years. Gilbert<sup>7</sup> stated that in a series of 22,810 necropsies performed at Bellevue Hospital in New York from 1904 to 1935 there was only one instance of primary epithelioma of the ureter proved at necropsy. There were no records in the clinical files of Bellevue Hospital of such a case. In a series of 16,565 malignant tumors encountered at the Memorial Hospital, Pack and LeFevre<sup>8</sup> apparently did not find any primary ureteral malignant growths.

The usual incidence of age in these cases varies from the fourth to the eighth decade and the average age in Gilbert's series of forty-one cases collected from the literature was 57 years. In our series the youngest patient was 37 years of age and the oldest patient was 71. The average age (for our series) was 56.1 years. There is no particular incidence by sex when the whole series of reported cases is considered, but there seems to be a somewhat greater prevalence of the condition among male persons. There were sixteen male and two female patients in the group of cases we are reporting.

## PATHOLOGIC CONSIDERATIONS IN RELATION TO RESULTS

The eighteen cases reported in this paper represent proved instances of primary epithelioma of the ureter. In each of them the kidney on the same side was carefully examined and no evidence of tumor was found in the renal pelvis. In five additional cases the diagnosis was primary epithelioma of the ureter but at operation the primary lesion was found to be a tumor of the renal pelvis. In another case a diagnosis of epithelioma of the ureter was made, but, because of the advanced age of the patient and the patient's general debility, surgical treatment was not advised.

All the tumors were graded according to the classification of Broders for vesical tumors: one was grade 1, nine were grade 2, seven were grade 3 and one was grade 4. In analyzing the results obtained in the treatment of tumors of various grades, the type of treatment instituted must be considered. Of the ten patients who had grade 1 or grade 2 tumors, one is living nine years, two are living three years, one is living two years and three are living one year or less after treatment at the time of this writing. One patient died fourteen months after operation and two patients could

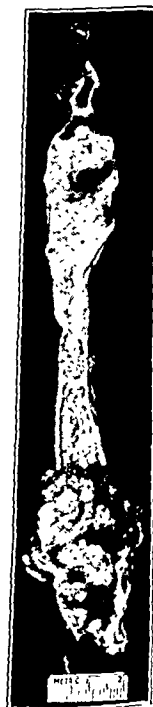


Fig. 1.—Gross specimen, showing epithelioma of the lower part of the ureter, with secondary dilatation of the ureter above the site of the lesion.

7. Gilbert, J. B.: *Studies of the Natural History of Genito-Urinary Tumors. I. Primary Cancer of Ureter: Autopsy Study with Review of the Literature*, *Am. J. Surg.* 36: 711-716 (June) 1932.

8. Pack, G. T., and LeFevre, R. G.: *The Age and Sex Distribution and Incidence of Neoplastic Diseases at the Memorial Hospital, New York City, with Comments on "Cancer Ages," J. Cancer Research* 14: 167-294 (June) 1930.

not be traced. One patient, who is alive two years after his operation for an extensive grade 2 lesion which measured 8 by 4 by 2 cm., associated with considerable periurethritis, was seen recently to have a large local recurrence and infiltration of the entire left wall of the bladder. The one patient who died within

In more than two thirds of the reported cases in a review of the literature, the site of the ureteral tumor was in the lower third part of the ureter. In our series the lesion was in this region in thirteen of the eighteen cases. In two cases the lesion occurred at the junction of the lower and middle third portions, and in three cases the tumor was in the upper third part of the ureter.

Clinical and Pathologic Data, Results of Treatment: Eighteen Patients Suffering from Primary Epithelioma of the Ureter

Case	Age, Years	Tumor		Treatment					Results		
		Diameter, Average, Cm.	Cautery, Excision of Tumor	Nephrectomy, Partial Ureterectomy	Subsequent Complete Ureterectomy, Partial Resection of Bladder	Complete Nephro-ureterectomy, Partial Resection of Bladder	Time of Last Follow-Up Data, Months Since Operation	Recurrent Tumors of Bladder	Survival, Months After Operation	Death, Months After Operation	
1	63	1	4	+	+	..	38	+	38	..	
2	54	..	..	..	..	..	116	+	116	..	
3	64*	2	2	..	..	..	14	+	..	14	
4	38	3	3	..	..	..	44	+	44	..	
5	56	2	2	..	..	..	†	..	..	..	
6	64	2	2.5	+	..	..	†	..	..	..	
7	47	5	5	..	..	..	25	+	25	..	
8	37	2	3.5	+	+	..	14	+	14	..	
9	71	2	4.5	..	..	..	4	..	..	..	
10	61	2	1	+	..	..	2	..	2	..	
11	40	3	4	..	..	..	30	+	..	30	
12	54	3	1.5	+	..	..	6	..	..	6	
13	63*	3	1	+	..	..	..	..	..	P. O.	
14	46	3	1	..	..	..	7	..	..	7	
15	57	3	..	+	..	..	92	+	92	..	
16	71	3	4	+	+	..	27	..	..	27	
17	62	3	4	..	..	..	9	..	9	..	
18	57	4	2	..	..	+	17	..	..	17	

\* Female.  
† Not heard from.  
‡ Huge inoperable mass.

Fig. 2.—Excretory urogram: a forty-five minute urogram showing pyelectasis, caliectasis and ureterectasis; the urogram is not diagnostic.

fourteen months after operation did not receive treatment which, in the light of present knowledge, would be considered adequate. The best form of therapy will be considered in the latter part of this paper. Seven patients had tumors which were graded 3 and one had a tumor graded 4. One postoperative death was caused by pyelonephritis in the remaining kidney. During the past year (1939) one tumor was explored and deemed inoperable. Of the remaining six patients operated on, two died within one year, one died within two years and one died within three years after operation. One patient is living, at the time of writing, eight years after operation. He has recently had gross hematuria, however, but has not returned to this clinic for subsequent examination. One patient could not be traced.

The smallest tumor was a little less than 1 cm. in diameter and was papillary in character. The largest tumor measured 8 by 4 by 2 cm. In five cases there was considerable periureteritis. The significant lesion found secondary to the tumor was dilatation of the ureter above the site of the lesion and in many hydronephrosis as well was present. Figure 1 is a picture of a gross specimen, showing the marked obstruction produced by the tumor of the ureter, with definite dilatation of the ureter above. Hydronephrosis in such cases can be mild or severe and can produce a palpable mass.

Metastases usually occur early if treatment has not been adequate, and these are found in the retroperitoneal glands, liver and lungs. The frequency with which similar lesions can be found in the bladder requires some comment. It is not our desire to discuss the theory of the multicentric origin of vesical, ureteral

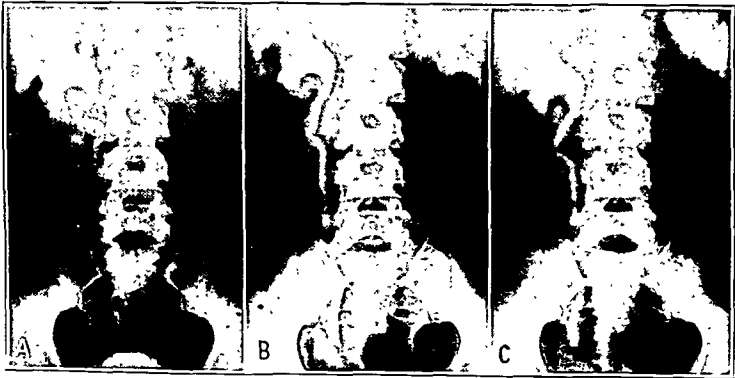


Fig. 3.—a, excretory urogram; a forty-five minute urogram showing (1) definite pyelectasis, (2) caliectasis and (3) ureterectasis (1 +) of the upper two-third portion of the ureter; the lower part of the ureter is not outlined; b, right retrograde ureteropyelogram, showing an irregular filling defect in the lower third part of the ureter, with dilatation of the ureter above; c, delayed urogram made twenty minutes after the retrograde catheter had been removed and the patient had been allowed to walk around; medium is still retained in the renal pelvis, calices and ureter.

and renal pelvic tumors or the theory of implantation of fragments of these neoplasms. However, we must call attention to the fact that these lesions have a tendency to recur in the bladder and each patient after operation should be instructed to return for periodic,

regular cystoscopic examination, as do patients operated on for primary vesical neoplasms.

Complicating pathologic processes are common in epithelioma of the ureter. We have already mentioned dilatation of the ureter and the renal pelvis. A not infrequent observation is secondary infection with pyonephrosis, and in a review of the literature associated

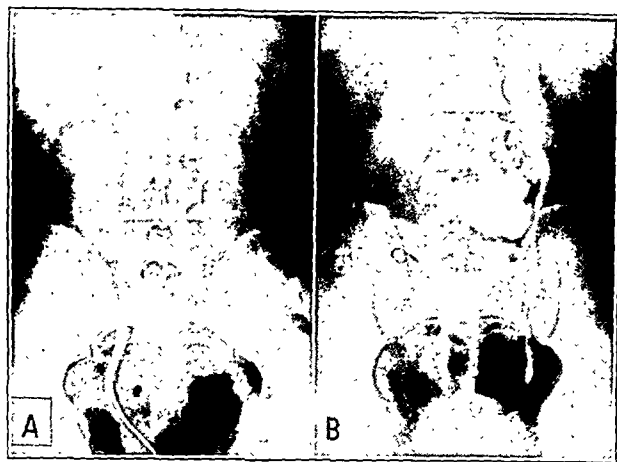


Fig. 4.—*a*, retrograde urogram of an opaque catheter in the right ureter; obstruction is at the level of the second sacral vertebra; the narrowed part of the ureter is situated just above the point of obstruction for a distance of 1 cm.; the ureter above is irregularly dilated (graded 2 to 3) and is tortuous; pyelectasis, grade 2+ and caliectasis, grade 1, are present; *b*, left retrograde ureterogram showing obstruction producing a filling defect in the ureter at the level of the third lumbar vertebra. No medium passed above the obstruction (the large, mottled, irregular shadow is a mass of calcified mesenteric glands).

calculi were found in approximately 15 per cent of cases. In three of our cases there was associated nephrolithiasis.

#### SYMPTOMS

Hematuria and pain are the predominant symptoms. A mass in the loin occasionally has been noticed when hydronephrosis is associated. Hematuria is usually the first symptom and may or may not be associated with pain. It occurred in sixteen of our cases and was the chief complaint in thirteen. Generally it is intermittent and begins without cause, but it may be associated with exertion or straining; the bleeding is marked and the blood is thoroughly mixed with the urine. Intense and colicky pain may be associated if there is formation of clots. These clots from the ureter usually are rather characteristic, being long and stringy and resembling a worm.

Pain of varying degrees has been noted. There may be none at all; a few patients will notice a dull, aching sensation in the loin, and a few will present a history of definite renal and ureteral colic. Pain may be the initial symptom; if it is, it shares importance with hematuria in this respect. In almost all cases it is one of the principal factors during the course of the disease.

The finding of a mass by the patient is noted in a small percentage of cases, and this mass is a hydronephrotic kidney secondary to the obstruction in the ureter produced by the primary neoplasm. Rarely, if ever, does the ureteral neoplasm itself produce a palpable tumor.

Occasionally the patient notices some frequency of urination, but the vesical symptoms usually are minimal. Backache is a rather common complaint.

#### DIAGNOSIS

Urinalysis, cystoscopy and urography, both excretory and retrograde, are of the utmost value in diagnosing ureteral neoplasm. The urine may contain erythrocytes, leukocytes (if infection is present), ureteral epithelium and fragments of tumor. The latter, if present, are very helpful in establishing the diagnosis of tumor but probably are found infrequently. Hematuria was noted in fifteen cases at the time of examination.

Cystoscopic examination may reveal an entirely normal bladder and normal ureteral orifices. Secondary cystitis may be seen if infection accompanies hydronephrosis. The ureteral orifice on the involved side may show evidence of an inflammatory reaction around it, manifested by a ring of edema with local redness, with or without erosion or distortion of the orifice. If the growth is situated low in the ureter, a bulging of the intramural ureter into the bladder may be noted, and in some cases the tumor mass or part of it may herniate through the ureteral orifice into the bladder. If obstruction from the growth is complete, no urine can be seen coming from the ureteral orifice on that side because the kidney may have become functionless. If the obstruction is not complete, the ureteral spurts of urine may be bloody or turbid. In one of our cases the jet of urine from the ureter was perfectly clear, but, when the catheter was passed up the ureter, bright red blood was seen to emerge from the orifice alongside the catheter. As Chevassu and Mock<sup>9</sup> suggested, bloody urine may be obtained from the ureter below the site of the tumor while clear or turbid urine, depending on whether or not associated infection is present, will drain from the catheter when it is passed above the tumor. This is a delicate procedure and may be valuable if it is satisfactorily carried out.

Excretory urography has been of great help in demonstrating the degree of function remaining in the kidney. If function still remains, the urogram will show whether or not secondary hydronephrosis or hydro-



Fig. 5.—*a*, fifty minute excretory urogram showing large soft mass of tissue in the right renal region, with no evidence of renal function; *b*, right ureterogram of ureteral stump, showing huge irregular filling defect in the lower third portion of the ureter.

ureter is present. Occasionally the point of obstruction may be clearly defined, with a dilated ureter above and little or no evidence of medium in the ureter below. However, a review of our own cases and also of those in the literature reveals that the diagnostic value of the

9. Chevassu, Maurice, and Mock, Jack: Epithéliome primitif de la partie moyenne de l'uretère, Bull. et mém. Soc. d. chirurgiens de Paris 3S: 522-533 (April) 1912.

excretory urogram in epithelioma of the ureter is not in actual demonstration of the lesion by showing the filling defect or the stricture in the ureter but rather in demonstration of the degree of function present. If function is present, the amount of dilatation of the urinary tract above the lesion will be shown in this urogram (figs. 2 and 3 *a, b* and *c*).

Retrograde pyelo-ureterography is necessary in most instances to show the actual deformity and its situation (fig. 4 *a*). When ureteral obstruction is complete and impassable to a catheter, a retrograde ureterogram will also demonstrate the point of obstruction by outlining the ureter below this point (fig. 4 *b*). Frequently the tumor will produce a filling defect in the urogram whether the urogram is excretory or retrograde, and this defect is characterized by a marked irregularity in the outline of the ureter at the site of the lesion, with or without dilatation of the ureter above, and a normal outline of the ureter below, the tumor.

Accuracy of diagnosis has improved as a result of excretory urography and in the majority of the cases in this series the need for an exact determination of the cause of pyelectasis was evident from the excretory urograms. Nevertheless the excretory urogram is notoriously lacking in its ability to outline the ureter in its entirety. As a result of this, exact evaluation of the underlying pathologic process producing the obstruction is not always possible without the making of retrograde urograms. Undoubtedly a number of patients suffering from epithelioma of the ureter have had a wrong diagnosis of hydronephrosis; the true diagnosis has been missed until such time as the patient has again presented himself with continuation of the hematuria. Two patients were operated on for hydronephrosis and the tumor in the ureter was found subsequently. In another instance the kidney was removed for hydronephrosis (fig. 5 *a*) and the patient returned later because of persistent hematuria. Cystoscopy was done and a ureterogram made of the remaining stump of the ureter. This procedure revealed a definite filling defect and a diagnosis of ureteral neoplasm was made (fig. 5 *b*). The diagnosis was confirmed at the time of operation. Again we wish to emphasize the importance of ascertaining the cause of existing hydronephrosis, particularly of patients more than 50 years of age.

#### TREATMENT

Numerous surgical procedures have been suggested as the proper means of treating tumors of the ureter. When a discussion of treatment of this condition is considered it must be realized that, although many observers refer to "benign papillomas" of the ureter in much the same way as they do to "benign papillomas" of the bladder, these tumors are neither benign pathologically nor benign clinically and must be considered as being malignant lesions if the desired results are to be obtained. For this reason we believe that the early suggestions of Marion,<sup>10</sup> Albarran and others regarding incision of the ureter over these so-called benign papillomas and destruction of them with surgical diathermy current are not sound and should not be practiced. In an early case of our own series in which the tumor was removed in this manner there have been frequent recurrences, finally necessitating nephrectomy, ureterectomy

and, more recently, resection of the bladder. This tumor was graded 2 on the basis of 4, according to Broders' classification.

It is possible, to be sure, to resect a segment of the ureter containing a small early malignant lesion and then to reestablish continuity of the ureter by end to end anastomosis, but the probability of recurrence is so great that such a conservative procedure is not justified. If it is imperative to conserve a functioning kidney on the affected side, such as would exist if solitary kidney was present or if a functionless kidney was present on the opposite side, in such circumstances the ureter should be divided well above the site of the lesion as near the renal pelvis as possible; permanent nephrostomy should be followed by complete ureterectomy and segmental resection of the ureterovesical orifice. In this connection it is of interest that three of our patients who had grade 2 lesions, and for whom segmental resection of the vesical wall containing the ureterovesical orifice and intramural portion of the ureter was not done, all suffered from recurrences in this region which required subsequent resection.

The reason for recurrence of the lesion in the bladder is a debatable question and does not come within the scope of this paper. However, it must be remembered that the lymphatic vessels of the ureter extend to the renal pelvis and the aortic glands and also anastomose freely across the base of the bladder. Also the iliac glands are directly connected to the lymphatic vessels of the lower third part of the ureter. It is reasonable to assume, on the basis of present knowledge of the growth of cancer, that in primary epithelioma of the ureter the lesion could grow by lymphatic extension and by direct extension down the ureter and directly through the walls of the ureter to contiguous structures. For example, intestinal obstruction has been reported to occur by direct extension from carcinoma of the ureter.

In view of these facts, certain surgical procedures for the management of primary epithelioma of the ureter definitely can be proposed to produce the best possible results. The operation of choice, if the lesion is operable, is total nephro-ureterectomy and segmental resection of that part of the bladder containing the ureterovesical orifice and the intramural portion of the ureter. The adipose tissue situated along the ureter should be carefully kept intact because of the likelihood that the cancer has extended to it.

The size and rate of growth of the lesion are definite factors which influence recurrence and mortality. For instance, a lesion which is large but slow in growth is wholly as formidable as a very small lesion of rapid growth, if not more so. An excellent illustration of this point is presented by our own case in which a lesion occurred in a ureter whose corresponding kidney represented complete aplasia. The lesion was slow in growth but measured 2 by 8 cm. Complete ureterectomy and segmental resection of the bladder were performed. The patient is still alive at this writing but has a massive local recurrence and his early death is inevitable. In the light of our experience to date it would appear that, if much extra-ureteral fixation is present, local recurrence can be expected and that all future efforts at eradication following complete excision should be extensive roentgen therapy directly over the original site of the tumor.

10. Marion, G.: De l'étiologie des papillomes de l'uretère, *J. d'urolog.* 8: 129-133, 1919.

The use of applications of radium has been advised by Hess,<sup>11</sup> who has constructed an apparatus and devised a method of applying radium directly up the ureter to the site of the lesion. We have not had experience with this procedure, but it would seem to us that if such a procedure could be successfully carried out it might be advantageous to irradiate the lesion locally and to follow this procedure with complete nephro-ureterectomy as offering a better chance of cure of some lesions.

Our usual procedure in performing nephro-ureterectomy is to expose the primary lesion through an inguinal incision, great care being taken to prevent separation of the fatty tissue from the lesion. The ureter is carefully separated down to the bladder. Segmental resection of the wall of the bladder, including the ureterovesical orifice and all adjacent fat, is performed. This portion of the ureter and the wall of the bladder is then covered with a large Penrose drain to prevent contamination of adjacent structures. The inguinal incision is closed and the patient is then turned in the kidney position. The kidney is then removed together with the attached ureter and segment of bladder, through the usual kidney incision. A course of postoperative roentgen therapy is advised because of the tendency for local recurrence within the bladder to occur. The patients are followed for a five year period, the same as is done with patients who have tumors of the bladder. We believe that if complete nephro-ureterectomy, together with segmental resection of the bladder, is performed in all cases in which the lesion is operable a greater percentage of cures will be obtained than has been obtained by other methods.

#### SUMMARY AND CONCLUSIONS

Primary epithelioma of the ureter is a comparatively rare disease, but it occurs sufficiently often that the possibility of such a condition's being responsible for hydronephrosis, especially if it is associated with hematuria, must be recognized. Hematuria is the outstanding symptom and the blood in the urine is often bright red.

Excretory urograms are valuable, if the kidney is still functioning, in that they reveal the extent of the pyelectasis, caliectasis and ureterectasis present, but they may or may not identify the obstructing lesion of the ureter. Retrograde pyelograms are essential to demonstrate the lesion in most instances and should be made whenever patients with hydronephrosis are of the "cancer age," if the cause is not definitely understood.

Treatment of the condition is surgical and surgical intervention should be instituted early. Complete extirpation of the kidney, ureter and the ureterovesical segment of the bladder should be done because of the tendency for the growth to extend through the wall of the ureter to adjacent structures, and all periureteral adipose tissue should be removed with the ureter.

The results of surgical treatment parallel closely the completeness of the operation, the degree of malignancy present and the operability of the lesion. Low grade lesions, although of large size, may be as great a hazard to the life of the patient as small, high grade lesions. Roentgen therapy should be administered postoperatively to all patients.

#### ABSTRACT OF DISCUSSION

DR. PAUL A. FERRIER, Pasadena, Calif.: In the Section on Pathology and Physiology of the American Medical Association two years ago, Dr. Foord and I presented a review of 133 cases and added six. To date there are 170 cases, all but fifty in the past ten years. We found hematuria, pain and palpable mass the most common leads to diagnosis. Hematuria is the most striking symptom and was absent in only eleven of 139. The next most common symptom, pain, was absent in only sixteen of 139 cases. The mass was most often the occluded kidney. But one should never neglect to palpate the lower part of the ureter. X-ray examination may show an obscure mass. Coincident stone is occasionally present. Metastases in bone and lungs may be seen. In more than half the cases excretory urograms showed no dye on the affected side. In cystoscopic study of eighty-one cases the ureteral tumor was visible in thirty cases, but only during peristalsis in two. Bleeding was seen from the meatus in twenty-six, congested meatus in seven and impassable obstruction to the catheter in fifty of the eighty-one. The catheter induced bleeding in seventeen, clear urine was obtained from beyond the tumor in three and there was associated tumor of the bladder in six. A good ureterogram may be hard to get. Most frequently the obstruction is impassable. There were only fifty-four correct diagnoses. All epithelial tumors of the ureter should be considered carcinoma. Histologically ureteral tumors are identical with those of the bladder and renal pelvis, but the rich lymphatics of the ureter and thin wall make extension beyond its origin of the same degree of malignancy much more rapid. All agree that the ideal treatment is nephro-ureterectomy with a cuff of bladder. If the cancer has widely invaded extra-ureteral tissues, resection is of doubtful value. Thompson-Walker, Bachrach and Thomas each resected tumors of the lower end of the ureter and transplanted the ureter into the bladder. Papin resected a tumor of the upper part of the ureter and transplanted the ureter into the pelvis. Wohlleben resected a small tumor of the ureter and did an end to end anastomosis, followed in a year by recurrence. The danger of recurrence outweighs conservation. In suitable cases a one stage operation is desirable, but in forty-four one stage nephro-ureterectomies the mortality was 40 per cent, while in twenty-two cases done in two stages the mortality was only 5 per cent. The prognosis is bad. Drs. Counsellor and Cook have one eight year cure. There are three others on record.

DR. MONROE E. GREENBERGER, New York: This type of urinary tract involvement had to await the development and refinement of urologic technic before antemortem diagnosis became possible; for this reason the vast majority of cases have been reported in recent years. The treatment is nephro-ureterectomy with segmental resection of the bladder containing the intramural portion of the ureter. This method is of greater value than resection of the tumor-bearing portion of the ureter not only because of the danger of recurrence or the possibility of multicentric foci but because the lymphatics ascend from the pelvic portion of the urinary tract along the ureter to the regional nodes near the kidney pedicle. It is therefore advisable to do a nephro-ureterectomy with removal of the periureteral and perirenal fat. A preoperative diagnosis, as shown by the authors, is not difficult when the possibility of ureteral tumor is kept in mind and a complete urologic survey is performed. The diagnosis in our case was comparatively easy, owing to the fact that blood was seen emanating from the ureteral orifice and, when the ureteral catheter was passed to the kidney pelvis, crystal clear urine was obtained. This finding, plus a "lobster claw"-like filling defect in the lower third of the ureter on retrograde pyelography, convinced us that the diagnosis was a tumor of the ureter.

DR. HUGH H. YOUNG, Baltimore: Recently I had a patient for whom complete nephro-ureterectomy was done by an excellent urologic surgeon. He divided and ligated the ureter where it entered the bladder. Only the intramural portion about 1 cm. in length remained. Nevertheless when the patient came to me there was a cauliflower-like tumor which had grown into the bladder from this remaining portion of the ureter. It looked like a strawberry and was approximately 2 cm. in diameter. It seemed desirable to do a very radical resection

11. Hess, Elmer: Tumors of the Upper Urinary Tract, Pennsylvania M. J. 42: 868-872 (May) 1939.



of the bladder wall and adjacent tissues. I felt confident that this could not be thoroughly done from above. I opened the bladder widely, inserted my self-retaining four bladed retractor, picked up the mucous membrane with forceps at a distance of 2 cm. from the tumor in every direction and made a circular incision around these forceps. At the upper inner portion the incision went down to the peritoneum, which was seen, picked up and opened. The finger was inserted, and against it the peritoneal wound was enlarged in each direction. In the lower portion the seminal vesicle was adherent and removed with the mass. A few bleeding points were tied, and the tissues above the bladder adjacent to the old operative wound were also excised. This left an opening in the peritoneum about 2 inches long and 1 inch wide. No difficulty was experienced in closing this with continuous plain catgut. The muscle and mucosa of the bladder were then approximated with continuous catgut. The whole operation was done through the bladder and was very radical in scope. Suprapubic drainage was provided. The patient's postoperative course was satisfactory. Since his return home six months ago he has continued to do well. I offer this transvesical intraperitoneal operation for radical removal of the lower end of the ureter, when it is involved, as the most thorough method of handling such cases.

DR. VIRGIL S. COUNSELLER, Rochester, Minn.: If I were to emphasize any part of the management of such patients, I would emphasize accurate diagnosis and then advise performance of nephro-ureterectomy in one stage unless certain difficulties are encountered, in which case the procedure would be most difficult. Also I feel that the low inguinal incision for the removal of the lower portion of the ureter and the segment of bladder should be ample. An ample incision will heal just as well as a small incision and, furthermore, it will facilitate the operation tremendously. I am delighted that Dr. Young brought out the fact that when a tumor of the type we are discussing does recur in the ureteral orifice, that is, a tumor which was not removed by segmental resection, the surgeon is faced with a very difficult problem. Moreover, no matter how radical the operation might be for secondary removal of such a tumor, the chances of cure are rather negligible.

## MORSUS HUMANUS

SIXTY CASES OF HUMAN BITES IN NEGROES

FRANK K. BOLAND, M.D.

ATLANTA, GA.

Trauma caused by human teeth (*morsus humanus*) may occur in two ways. The assailant may be the victim when his knuckles come in violent contact with the teeth of the person receiving the blow, or the victim may be the one who is actually bitten by another individual. The two methods of injury are responsible for about the same number of reported cases. Strictly speaking, trauma to the clenched fist is not an actual bite, but it is a more civilized manner of producing the lesion. Deliberately burying one's teeth into human flesh is reminiscent of primeval savage instincts, if not cannibalism, and impels us to camouflage "human bite" with the milder Latin "*morsus humanus*."

The remarkable feature of *morsus humanus* is the virulent, destructive trauma which so often follows an apparently trivial wound. Mason and Koch,<sup>1</sup> in their exhaustive paper, mention three factors which cause the excessive, and sometimes permanent, damage or death. These factors are, first, the virulence of the pathogenic organisms; second, the method whereby infection is

conveyed along tendons and tendon sheaths, and, third, the complicated arrangement of joint capsules and facial planes which are difficult to free from infectious processes. The role played by these agencies is well illustrated in the series to be reported. As a matter of fact, while the cases considered here show bites of the face, ear and arm, 36 in number, the only injuries which

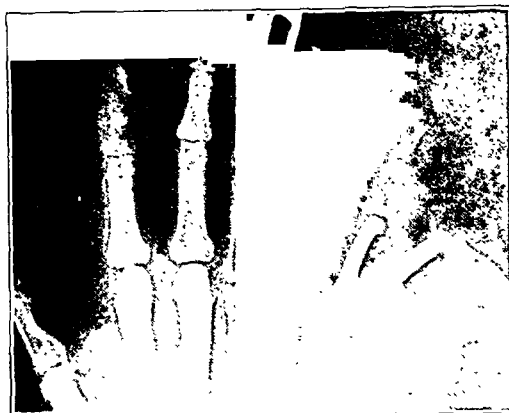


Fig. 1.—Osteomyelitis of forefinger from morsus humanus.

resulted seriously were those of the fingers and hand, 24 in number.

Various bacteria found in the mouth were recovered from wounds inflicted by teeth. Such bacteria were staphylococci, streptococci, colon bacilli, the fusiform bacilli and spirochetes of Vincent, and others. The symbiotic action of the two last mentioned make them especially dangerous. There is an interesting analogy between the effects produced by these organisms and the effects of gas-forming bacteria. Both are anaerobic at this time, both act only on devitalized tissue and both give forth a malodorous, characteristic odor. Hennessy and Fletcher<sup>2</sup> found that the organisms of Vincent do not multiply when inoculated under healthy skin but only after the skin has been injured.

In regard to the two other factors described by Mason and Koch, when the clenched fist strikes the teeth and gums, at the moment of impact the tendon sheaths, tendons and other tissues of the extensor area of the fingers are stretched to full length. The skin over the knuckle is penetrated, and the tendons and possibly the joint are exposed. As the fingers are then straightened the damaged parts relax, and extension carries infection deep into the tissues. Three spaces soon become involved, the joint space, the dorsal subcutaneous space and the dorsal subtendinous space between the tendon and the capsule. Thus the growth of anaerobic germs is accelerated.



Fig. 2.—Morsus humanus of thumb, which led to amputation.

### REPORT OF CASES

The present paper was prompted by the observation of 60 cases of *morsus humanus* among the patients of the Negro division of the Grady Hospital (Emory University) during the past year. Such cases among the white patients were rare.

From the Department of Surgery, Emory University School of Medicine.

Read before the Section on Surgery, General and Abdominal, at the Ninety-First Annual Session of the American Medical Association, New York, June 13, 1940.

1. Mason, Michael L., and Koch, Sumner L.: Surg., Gynec. & Obst. 51: 591-625 (Nov.) 1930.

2. Hennessy, P. H., and Fletcher, William: Lancet 2: 127-128 (July 17) 1920.

While the records of the early periods of the institution are incomplete, the impression exists that infected wounds from human bites among Negroes are more virulent today than formerly. The reason is believed partly to be the fact that the teeth and gums of the



Fig. 3.—Débridement which saved thumb.

Negro, who now eats more so-called civilized foods, harbor more disease than during the days when he subsisted on rougher, cleansing articles of diet such as cabbage and turnip greens. It is difficult to locate a "biter." Only three in this group were found and examined. Two of these had bitten into finger joints, and one had bitten a woman on the cheek and arm. In one of the first cases cultures and smears showed the fusiform bacilli and spirochetes of Vincent, staphylococci and streptococci; the second case showed only the later two organisms. Both bites in these instances caused serious damage to the fingers, and the same kind of bacteria, plus others, were recovered from the wounds that were discovered in the teeth and gums of the "biters." The teeth of the third "biter" also showed the two forms of Vincent's organisms, but the wounds on the cheek and arm of the victim healed with but little infection.

Women furnish the larger number of patients with morsus humanus, and in this series 43 patients were female and 17 were male. The anatomic distribution was as follows: face, 24 cases; fingers, 24; hand, 3; ear, 2; arm, 7. As already mentioned, wounds of parts other than those of the fingers and hand produced only



Fig. 4.—Morsus humanus of lower lip two hours after infliction of wound.

symptoms such as would follow an ordinary abrasion or laceration, although it is conceivable that virulent infection might follow bites in any portion of the body. The worst results followed trauma made with the clenched fist or bites which opened joints and tendon

sheaths. The patients were first seen in the clinic from a few hours to eight days after receiving the injury and had been given various forms of treatment or no treatment. If the wound was recent, no evidence of inflammation or suppuration was present; if one or more days had elapsed since injury was inflicted, redness, swelling, localized heat and tenderness existed. Lymphangitis and metastatic adenitis may have developed. Stiffness of fingers caused by pain or swelling was a common symptom. In some cases a seropurulent, foul-smelling discharge produced the characteristic disagreeable odor. On roentgen examination, six patients later showed osteomyelitis of the phalanges. There might be septicemia, with high fever. A prolonged course resulted in ill patients requiring hospitalization. Although 40 per cent of the patients admitted to this hospital give positive Wassermann or Kahn reactions, it could not be determined that syphilis was transmitted in any of these cases of human bite.

#### END RESULTS

One patient lost the last phalanx of a finger, two patients had whole fingers amputated, and another lost her thumb and forefinger. Several patients returned to



Fig. 5.—Blue-gummed Negro patient with normal flora of teeth and gums.

the clinic with deformity or ankylosis. There was one death:

A Negro woman aged 38 received a human bite of the terminal phalanx of the left forefinger eight days before admission to the hospital. The finger became swollen and tender the next day, and the disease had spread until the whole hand was involved. She had treated the lesion with hot epsom salt dressings but did not consult a physician before entering the hospital. The patient had slight exophthalmos and moderate enlargement of the thyroid gland. The blood pressure was 120 systolic and 80 diastolic. The basal metabolism was not taken. The temperature was 102 F., the pulse rate 120 and the respiratory rate 30. The leukocytes numbered 31,600. Operation under nitrous oxide-oxygen was done the day after admission, through several multiple incisions extending into the palmar surface of the hand, 20 cc. of thick pus being evacuated. Through and through drainage was established. The next day incisions were made on the radial and ulnar sides of the forearm and connected by blunt dissection. The cuts in the hand were opened wider. Carrel-Dakin tubes and treatment were instituted. The patient's condition continued to grow worse and four days later all incisions were again enlarged and thick necrotic material was removed. The index finger was entirely gangrenous and was amputated. The patient was given two blood transfusions. About one month after injury she began coughing and expectorated foul smelling sputum suggesting lung abscess, which was confirmed by roentgen

examination. The sputum was negative for tubercle bacilli. The patient grew progressively worse and died two months after injury.

#### TREATMENT

No standard treatment has been established because none has given uniformly good results. On account of the bad reputation of morsus humanus of the fingers and hands, the moment it is known that the wound was made by human teeth radical treatment is begun. There is never any effort on the part of the patient to hide the cause of the injury. On the contrary, he wishes to tell all about it. If the wound has been sutured it is opened and swabbed with phenol or packed with sulfanilamide crystals. At the same time sulfanilamide is prescribed by mouth. If the patient is hospitalized the Carrel-Dakin technic usually is carried out. Old wounds are debrided, which procedure I believe is better than the use of nitric acid, the actual cautery or roentgen rays. I have had no experience with arsphenamine or the zinc peroxide applications of Melaney.

#### THE BLUE-GUMMED NEGRO

For many generations a superstition has existed in the South that the bite of a "blue-gummed" Negro is poisonous and necessarily fatal. Such an idea is so firmly fixed in the minds of certain classes of the Negro population that they exonerate the killing of a blue-gummed Negro by the victim of the bite. It is considered justifiable homicide.<sup>3</sup> The danger from this injury has no scientific basis, but an effort was made in this study to examine the gums of such persons for evidences of "poison." Blue gums were found to be very common and were more marked in full blooded individuals than in mulattoes. The discoloration, known as melanoplakia, usually is confined to the gums of the incisor and canine regions. No reason is assigned for the existence of the anomaly except that of a racial characteristic. Among 32 patients examined by Dr. H. J. Harpole in the Negro clinic of the Atlanta-Southern Dental College, differentiation was made between congenital blue gums and blueness due to lead and bismuth poisoning. According to Dr. Harpole, in this day of the bismuth treatment of syphilis, bismuth poisoning has become extremely common, and he has recorded 200 cases in his clinic during twelve months. Recognition of the conditions is easy inasmuch as blue gums caused by lead or bismuth poisoning are swollen, red, tender and bleeding and give forth a fetid odor, whereas normal blue gums present none of these symptoms. In discoloration due to bismuth the blueness is shown as a thin line close to the teeth, and the tongue is very sore.



Fig. 6.—Blue-gummed Negro patient with fractured mandible. Innocuous bacteria recovered from gums.

On the other hand, the mouth of the typical blue-gummed Negro usually is otherwise negative or presents only the oral flora found around most teeth and gums. In 20 patients with blue gums from whom cultures and smears were taken only the usual innocuous bacteria were recovered, and as a matter of fact the teeth and gums of these persons appeared cleaner and more normal than the teeth and gums of Negroes without blue gums. Smears from the other 12 patients revealed Vincent's organisms, but the Negroes appeared to possess average teeth. From this study, therefore, it is fair to affirm that the bite of a blue-gummed Negro is no more dangerous than the bite of a member of the race whose gums are not blue. The appearance of the two kinds of gums under the microscope is identical. The impression has prevailed that Negroes are blessed with unusually good teeth, but dental authorities state that this is another exploded tradition. Their teeth look white in comparison with their black skin.

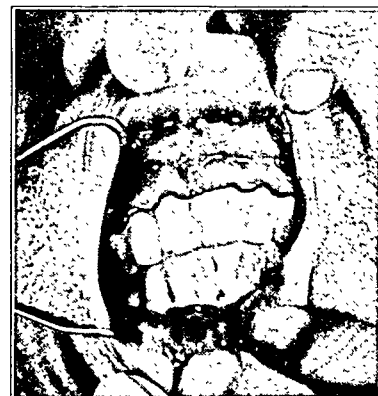


Fig. 7.—Thin blue line on gum, indicating physiologic or poisonous action of bismuth.

#### HOW CLEAN IS A HOUND'S TOOTH?

Consultations with Dr. C. C. Rife and other veterinarians show that as long as the hound is allowed to eat his usual rough food, including plenty of bones, his teeth and gums remain free from infection and necrosis but that when coddling begins and the dog is fed soft foods his teeth decay like those of human beings. It has been a noteworthy observation that the wound made by the bite of a dog rarely becomes infected although the dog may have rabies and may transmit it to its victim. Perhaps if the dog bite exposed a dorsal knuckle, serious infection would ensue as in a human bite. A dog bit a veterinarian's nose, leaving a gaping



Fig. 8.—Dog fed on soft food, with pyorrhea and loss of most teeth. Vincent's bacteria present.

wound. The wound was swabbed with a mild antiseptic and sutured tightly, no infection resulting. The dog was killed and found to have rabies. Inspection of a dog's mouth shows how normal food maintains cleanliness. The teeth are widely spaced, and rough articles of diet

3. It is said that the reason for the fear of the bite by a blue-gummed Negro is the idea that blue gums are caused by the administration of mercury given in the treatment of syphilis.

prevent the accumulation of injurious substances. Smears made from dogs with apparently clean mouths demonstrated about the same organisms generally found in normal human mouths, staphylococci, streptococci and sometimes Vincent's bacteria.

#### CONCLUSIONS

The principal conclusion to be drawn from a consideration of morsus humanus is to pay tribute to Mason and Koch for their historical contributions to the subject. Without the knowledge which their experiments and clinical experience have furnished, the course of events following this trauma to the clenched fist would still be but little understood. Their description of the three factors involved in the destructive and dangerous lesions which result from apparently mild trauma is a matter of the greatest importance. The pathologic processes taking place in tendon sheaths, joints and fascial planes make such injuries from human teeth an entity. Human bites of other parts of the body, exclusive of the hand, present no problems different from abrasions and lacerations from other causes. Praise for the authors of this paper, published ten years ago, should include the founder of their School of Surgery of the Hand, the late lamented Allen B. Kanavel, a



Fig. 9.—Hound with clean teeth and gums. No pathologic bacteria present. Note wide spacing of teeth.

former chairman of this section. The enormous value which the work of these men ascribe to the human hand creates of this collection of anatomic tissues one of the paramount organs of the body, rivaling in usefulness, especially to the surgeon, any other organ or system. Such an aid to our art and science as the hand is worthy of the most meticulous care. In the present instance the matter appears to deal with the care of the teeth and the prevention of morsus humanus. The fellow who formerly carried brass knuckles was wiser than he knew.

478 Peachtree Street, N. E.

#### ABSTRACT OF DISCUSSION

DR. MICHAEL L. MASON, Chicago: A discussion of human bite injuries with men interested in the hand clinics in many of the large charity hospitals reveals that such wounds are by no means infrequent. Koch and Allen at the Cook County Hospital see approximately 75 cases a year. Of all bites, that of the human animal is the worst. The bite of the cat, the camel and the monkey rank next to the human bite in seriousness. The term human bite is somewhat of a misnomer since a great many of the bites are tooth wounds received on the knuckles during a fist fight. Important factors in the infection are the extent and depth of the wound, the crushing and devitalization of the tissues, and the types of the micro-organisms

introduced. Deep penetrating wounds in which the fascial planes, joints and tendon sheaths are invaded invariably give rise to most serious processes unless they can be seen early and cleanse and debrided extensively and thoroughly. The human mouth harbors a multitude of pathogenic and nonpathogenic bacteria already acclimated to growth in human tissues and fluids. They may proliferate and become invasive almost as soon as they are deposited and are already thriving before the body can muster forces against them. The evidence also seems conclusive that many of the organisms thrive well in symbiosis and that this is an important factor in the infection. Wounds of the trunk, breast, face and genitalia are relatively benign in comparison to those of the hands and fingers, a fact probably associated with the circulation of the area involved. It has seemed to me that we are dealing with a nonspecific infection and that several clinical pictures are produced. The bacteriology of infections from mouth bites is becoming better understood. For many years the process was looked on as a Plaut-Vincent infection. Careful studies with anaerobic as well as aerobic methods have shown that anaerobic and microaerophilic streptococci play an important role. It seems likely that infections from mouth bites owe their severity and characteristic manifestations to symbiosis of streptococci of this type with other bacteria from the mouth. On this phase of the problem we must look to Dr. Meleney for enlightenment. As to treatment, we must differentiate between the case seen early and that seen after infection has become well established. In the early case my own preference is for careful and thorough cleansing with soap and water, excision of crushed tissues and leaving the wound open. Bed rest, splinting and a warm moist pack will then give the patient the best chance of escaping a severe infection. In the late case, adequate drainage and the use of zinc peroxide by the technic of Meleney have yielded the best results of any treatment so far used.

DR. FRANK L. MELENEY, New York: In all these cases mouth bacteria are deeply introduced into the tissues, and retracting muscles or tendons have withdrawn them into the depths of the wound, where anaerobic bacteria have a predilection for growing. There is another group of cases in which these organisms are indirectly rather than directly introduced. A case has been reported which started from a blister pricked with a knife blade which had just been used for picking the teeth, and I have seen a case caused by a man suddenly thrusting his hand into his trousers pocket where there was a loose toothpick which he had used sometime before. That hand bites are more disastrous than those in other parts of the body is partly due to the fact that injured fascia, ligament, tendon and bone offer a particularly favorable environment for the organisms. These are the nonhemolytic anaerobic streptococci, the fusiform bacilli and spirochetes. They are not only anaerobic but have a definite synergistic action, making the combination of these organisms much more virulent than the pure cultures of the same organisms. The fusiform bacilli and spirochetes are so closely bound together that Tunnicliff could not be sure that they were not phases of the same organism. Knorr reported that he had never seen fusiform bacilli or spirochetes without anaerobic streptococci, and this has been my experience. This clearly indicates the importance of anaerobic bacteriology in any study of these cases. I have yet to see a report of a large series of these cases in which adequate anaerobic bacteriologic studies had been done. In the hospital with which I am associated these cases have been relatively few and we have not reported a complete series. The anaerobic bacteria and the damage which they can do if left in the wound must be constantly kept in mind. Removal consists of complete débridement as soon as the patient comes to the surgeon, no matter at what period of time after the injury. After débridement the wound should be flooded with a creamy suspension of active medicinal zinc peroxide in distilled water, covered with a layer of cotton soaked in the same material, then a layer of cotton wet with water, and then sealed with several layers of petrolatum gauze or sheet rubber to prevent evaporation. We have used it routinely and it has been frequently suggested in reports since then. Maier at Bellevue Hospital reported a series of human bites and obtained good results with zinc peroxide, but his supply gave out and he treated his subsequent cases with arsphenamine, with less success.

DR. CLAUDE E. WELCH, Boston: Several years ago in the Massachusetts General Hospital we encountered a series of rather severe tooth lacerations of the finger. Prompted by the number of stiff and amputated fingers that resulted, we made a study and laid down principles of treatment to be followed. There is no doubt about the wisdom of very early and adequate drainage. The only contraindication to immediate drainage is spreading lymphangitis. If this is present, the patient must be given hot packs for a short time and then operation performed as soon as it has subsided. Provided operation is undertaken, as Dr. Mason has pointed out, there is a great deal of variation in technic, depending on whether the patient arrives for treatment early or late. We have had a good deal of success in early cases with Bates's method of excision with the electrocautery, but in late cases the anatomic details of the fingers makes wide excision extremely difficult. The principle of operation is careful exploration under a tourniquet, so that all anatomic details will be observed. It is essential that any laceration of the joint capsule, pin point though it may be, must be detected at this time if a successful result is to be obtained. An immediate smear and culture is taken at the same time. If the capsule is opened, two collar incisions in the adjacent web spaces should be made to provide adequate drainage. I believe that lacerations of the tendon and infections of the subcutaneous spaces can be dealt with adequately but that joint infections undiscovered for several days will lead to stiff joints and amputations. I have found that zinc peroxide has been of value, but it must be remembered that zinc peroxide and also some of the newer drugs are to be regarded as only adjuvants to radical surgical therapy rather than alternatives. These cases are not common. The metacarpophalangeal joint was involved in 18 cases in our series. Four fingers were amputated before this study was started. Since that time none have been lost.

### *Clinical Notes, Suggestions and New Instruments*

#### CHEILITIS FROM SENSITIVITY TO OIL OF CINNAMON PRESENT IN BUBBLE GUM

JEROME MILLER, M.D., PHILADELPHIA

This case is being presented because of its unusual predilection and interesting etiology. It is a case of contact-type hypersensitivity involving the mucous membrane of the lips and is due not to direct contact with the agent per se but with the vapors of the oil.

P. I., a woman aged 25, was referred to me because of a cheilitis of six months' duration. At the time there was thought to be some relationship between the patient's fur coat and her symptoms, a fact which subsequently proved to be erroneous.

The eruption when first seen presented a swelling and mild erythema about the lips. The lips themselves were swollen, rough, fissured and scaly, and the patient complained of an itching and burning sensation. Closest scrutiny did not reveal the presence of vesicles. The lesions did not occur elsewhere on the body. She had been treated previously with various local topical applications, which did not seem to improve her condition. The personal and family histories were negative for any atopic manifestations.

The patient has been associated with a chewing gum firm in an executive capacity for the past two years. During this time she had as part of her duties the daily inspection of the factory. During her first year at the plant the flavoring agent that was used in the manufacture of the gum was bought in a prepared state. In September 1938 the firm decided to manufacture its own flavoring agent. Late in November 1938 the patient began to spend about 75 per cent of her time in the factory, working at various formulas that might be used in the flavoring of the gum. This did not necessitate her coming

in contact with the ingredients used. A formula was finally arrived at and about five weeks later, in December 1938, she first noticed an eruption of the lips.

The patient was then studied and routine intradermal tests to the various foods, inhalants, pollens and environmental allergens all proved to be uniformly negative, with the exception of an unexplained marked cutaneous reaction to silk. When a retest was made to silk at a later date the marked cutaneous reaction was still present.

Patch tests were then performed with the patient's personal objects. Negative tests were obtained to her fur coat, lipstick, pomade, powder, tobacco and tobacco paper. Since the reason for the positive reaction to silk on intradermal testing was not understood, patch tests were done with green, black and pink silk. All patch tests were negative. Negative patch tests were also obtained to 2 per cent paraphenylenediamine and 5 per cent methyl orange.

The next patch tests were performed on possible environmental and occupational allergens. Samples were obtained of all the individual ingredients that entered into the manufacture of the gum. Patch tests to cane sugar, corn sugar, corn starch, dried milk solids, ethyl butyrate, extract of vanillin, precipitated chalk, base, cumar resin and erythrosin paste were all negative.

The flavoring agents used in the chewing gum were next tested and a marked patch reaction was obtained to the composite flavor. Being fortunate enough to be able to obtain the individual constituents of the flavoring compound and their percentages, a breakdown of the flavoring agent was possible. The individual flavors were tested and a marked patch reaction was obtained to oil of orange and oil of cinnamon (oil of cassia) in concentrated solutions. All the other flavors in concentrated form failed to produce a positive reaction. Subsequently the oil of orange proved to be a primary irritant. The 1 per cent oil of cinnamon produced a slightly positive reaction, whereas the 2 per cent solution produced a definitely marked reaction within twenty hours. The vehicle used to dilute the oils in all cases was alcohol. Eight normal controls were patch tested with the 2 per cent oil of cinnamon and in all negative reactions were obtained.

The problem then resolved itself into explaining how the symptoms could have developed without having the patient actually come into direct contact with the offending substance, and how this fact could be proved. The supposition was then entertained that the hypersensitivity must have occurred from contact with the vapors that were given off by the volatile oil. Proof of this was furnished by using a modification of the pill box method described by Baker, which for want of a better term I have named the fume test. Using this method I again tested the patient with the 1 per cent oil of cinnamon and obtained a markedly positive reaction within seven hours (fig. 1), characterized by a vesiculobullous eruption with a surrounding erythema. During the time the fume test was in contact with the patient's skin she complained of a tingling and itching sensation of the lips, but without any visible lesions.



Fig. 1.—A, reaction to fume test with 1 per cent oil of cinnamon and B, to fume test with 2 per cent oil of cinnamon.

In performing the fume test, the supposedly offending substance must be a volatile agent. The lid of a small metal ointment box which has been previously perforated a number of times is placed on the bottom of a larger metal ointment box. A small piece of absorbent cotton is then moistened with the substance to be tested and placed underneath the perforated lid, which is held on the bottom of the larger box by means of adhesive tape. By using this procedure it will be seen that, when the box is inverted so as to come into contact with the skin, the smaller perforated box will hang suspended and not touch the skin. Sufficient care must be taken that contact is air tight and that there is no leakage which might allow the fumes to escape and thereby give the impression of a negative reaction. If care is also taken that the cotton is not saturated, any reaction that may ensue will be the result of the fumes which escape through the perforations to reach the hypersensitive skin, to produce a positive reaction (fig. 2).

Has desensitization been resorted to and has the patient's eruption improved? The patient agreed with me that, since the vacation period was at hand, improvement would occur if she would avoid the causative factor. This is precisely what has occurred. With the return of the fall season, however, the lips continued to remain in their improved state. This is so because the patient has given up entirely her daily inspection trips through the factory and has made only two uneventful hurried trips into the factory itself since last July—the time when her lips healed completely. Another important factor in her improvement is that, whereas formerly all gums that were manufactured contained oil of cinnamon, now about 25 per cent of the entire production is oil of cinnamon—a reduction of 75 per cent with the offending specific substance. For these reasons there was no need to resort to specific desensitization.

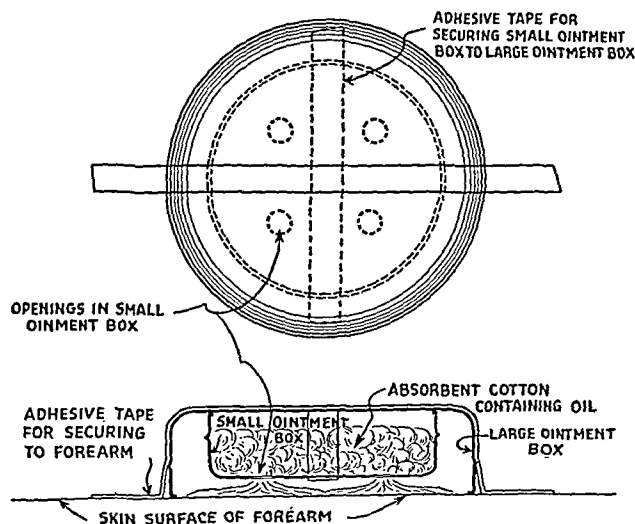


Fig. 2.—Sketch of apparatus used for fume test.

Oil of cinnamon is the volatile oil distilled with steam from the leaves and twigs of *Cinnamomum cassia* (Linné) Blume (family Lauraceae), rectified by distillation. It has as its chief constituent not less than 80 per cent by volume of cinnamic aldehyde. It is a yellowish or brownish liquid and has the characteristic odor of cinnamon. It is soluble in an equal volume of absolute alcohol.

There are two oils of cinnamon in commerce: one procured from the Ceylon cinnamon, the other from the Chinese cinnamon. The latter (oil of cinnamon) is now the only official one.

Oil of cinnamon is used as a flavoring agent to promote the palatability of various pharmaceutical preparations. It is used to render food more palatable and also as a food preservative by preventing the growth of molds. It is used as a carminative and to stimulate the appetite. It is incorporated in candies, chewing gum, tooth powder and cosmetics. It is also used in insecticides, mouth washes and antiseptic nasal oil sprays. It is incorporated in the official preparations of Elixir Vanillini

Compositum, N. F., Nebula Mentholis Composita, N. F., Spiritus Cardamomi Compositus, N. F., and Fluidextractum Cascaræ Sagradæ Aromaticum.

#### CONCLUSION

In the first case to be reported of cheilitis due to hypersensitivity to the vapors of the oil of cinnamon present in bubble gum, the eruption was limited solely to the lips. Hypersensitivity was demonstrated by the patch test and by the fume test. Complete amelioration of symptoms followed avoidance of the oil of cinnamon.

1920 Pine Street.

## Special Article

### GLANDULAR PHYSIOLOGY AND THERAPY

#### THE ANTIHORMONES

DAVID L. THOMSON, PH.D.

JAMES B. COLLIP, M.D.

AND

HANS SELYE, M.D.

MONTREAL, CANADA

*This special article is published under the auspices of the Council on Pharmacy and Chemistry. It is one of a series which will be published in book form as the second edition of "Glandular Physiology and Therapy." The opinions expressed in this article are those of the authors and do not necessarily represent the views of the Council.—Ed.*

At the present time the term "antihormones" is most commonly applied to certain substances of unknown origin which appear in the serum of animals treated for long periods with certain anterior pituitary extracts, which apparently explain the observed gradual loss of responsiveness to such extracts and which are capable of making other animals, previously untreated, refractory to treatment with similar extracts. The demonstration of an antihormone of this type thus involves at least three groups of animals: first, those from which the original anterior pituitary extract is prepared; second, those to which this extract is administered until they become refractory to it and the antihormone is present in their serum; third, those to which the serum is administered and which then show partial or complete inhibition of their usual response to an anterior pituitary extract identical with or similar to that used in the first place. Extracts from endocrine organs other than the anterior lobe of the pituitary may also be found to decrease in efficacy when administered over long periods, and in one or two instances the serum of the treated animals may acquire inhibitory properties and be said to contain an antihormone. Various modifications of this term have been used in other senses as well. The subject has been reviewed several times within the last few years.<sup>1</sup>

#### THE ANTITHYROTROPIC SUBSTANCE

When animals of various species are treated for long periods with anterior pituitary extracts containing the thyrotropic factor, the induced morphologic and physiologic signs of hyperthyroidism gradually wane and may indeed be replaced by signs of moderate hypothyroid-

From the Department of Biochemistry, McGill University.  
1. Collip, J. B.: Recent Studies on Anti-Hormones, *Ann. Int. Med.* 9: 150-161 (Aug.) 1935. Rambert, Paul: Le problème des antihormones, *Paris méd.* 1: 345-351 (April 22) 1939. Collip, J. B.; Selye, Hans, and Thomson, D. L.: The Antihormones, *Biol. Rev.* 15: 1-34 (Jan.) 1940.



ism.<sup>2</sup> (In the English sparrow, however, no such refractory state has been observed.<sup>3</sup>) If the treatment is stopped, the animals may gradually regain their original sensitivity in from four to six months.<sup>4</sup>

Collip and Anderson<sup>5</sup> showed that the refractory state was not due to exhaustion of the thyroid under overstimulation, since thyroid tissue transplanted from a normal into a refractory animal was itself refractory; and they showed that injections of the serum of the resistant rats into untreated hypophysectomized rats prevented the normal response (increased metabolic rate) of the latter to treatment with the thyrotropic extract. They obtained similar antithyrotropic serums by treatment of guinea pigs, dogs, rabbits and horses. Long before this, Masay,<sup>6</sup> in a neglected paper, described cachexia in animals treated with the serum of rabbits or guinea pigs which had been pretreated with pituitary suspensions, comparing the condition with that following thyroidectomy and stating that it was accompanied by exophthalmos.

Collip and Anderson pointed out that their antithyrotropic substance had no power to inhibit the thyroid hormone, although it appeared to influence the metabolic rate rather than the structure of the thyroid in their animals. But pretreatment with antithyrotropic serum was later found to prevent the histologic signs of thyroid activation<sup>7</sup> and the increase in thyroid weight<sup>8</sup> normally observed in young guinea pigs (or chicks<sup>9</sup>) treated with thyrotropic pituitary extract. Such tests are probably preferable to those based on metabolic rate, which may be influenced by the specific metabolic principle of the pituitary,<sup>10</sup> to which no resistance is developed. During continued treatment with thyrotropic pituitary extract the metabolic rate of the rat passes through a maximum about the end of the first week and by the fifth week has fallen to levels as low as those seen in hypophysectomized animals;<sup>5</sup> the antithyrotropic activity of serum has been found maximal at the fifth week in sheep<sup>11</sup> and at the tenth week in rabbits;<sup>12</sup> thereafter it declines. At the peak 2 cc. of the rabbit serum will inactivate

a dose of thyrotropic pituitary extract otherwise sufficient to double the thyroid weight of immature guinea pigs.<sup>12</sup>

The antithyrotropic substance seems to show marked but not absolute species specificity; rabbits and guinea pigs which had become refractory to bovine thyrotropic extract still responded to similar extracts from anterior lobes of pig pituitaries, and vice versa;<sup>13</sup> and the antiserum obtained from rabbits treated with a bovine extract did not prevent the response of guinea pigs to a thyrotropic fraction from anterior lobes of human pituitaries.<sup>14</sup> It is also stated that purified thyrotropic fractions prepared by flavianic acid precipitation may be administered for long periods without development of a refractory state, and are effective in guinea pigs that have become refractory to cruder fractions prepared by salting out.<sup>15</sup> All these observations have naturally been regarded as evidence that the antithyrotropic substance is a true antibody, produced as a response to the foreign protein present in the thyrotropic extracts. Not easily reconciled with this view are the observations that an antithyrotropic serum, administered by itself, will depress the metabolic rate of the rat<sup>5</sup> or the rabbit<sup>16</sup> and flatten thyroid epithelium in the guinea pig (Eitel and Loeser<sup>7a</sup>). Still more serious is the objection that antithyrotropic substance has been detected in the serum of normal, untreated animals of various species, including the dog,<sup>17</sup> sheep (Eitel and Loeser<sup>7a</sup>), rabbit<sup>18</sup> and man,<sup>19</sup> which seems to prove it to be a normal constituent of the body, unless this is not the same substance as the one found in larger amounts in treated animals. Antithyrotropic activity has been recognized in the serum of animals treated with an anterior pituitary extract which had little or no thyrotropic potency.<sup>20</sup> The nature of the antithyrotropic substance is perhaps less important than the fact that this substance must be expected to appear in the serum of patients treated with thyrotropic anterior pituitary extracts for long periods.<sup>21</sup>

The antithyrotropic substance is destroyed by boiling<sup>5</sup> and is apparently associated with the pseudoglobulin of the serum;<sup>8</sup> it may be purified by adsorp-

2. Aron, Max: Action combinée de la thyroxine et de l'extrait pré-hypophysaire sur la thyroïde chez le cobaye, *Compt. rend. Soc. de biol.* **104**: 96-98, 1930. Loeb, Leo, and Friedman, Hilda: Changes in Weight of Thyroid Gland of Young Guinea-Pigs Under the Influence of Acid Extract of Anterior Pituitary, *Proc. Soc. Exper. Biol. & Med.* **29**: 14-16 (Oct.) 1931; Long Continued Injections of Acid Extract of Anterior Pituitary on Thyroid Gland and Sex Organs, *ibid.* **29**: 172-174 (Nov.) 1931.

3. Miller, D. S.: Lack of Refractoriness to Prolonged Thyrotropin Administration in Birds, *Proc. Soc. Exper. Biol. & Med.* **38**: 453-455 (May) 1938.

4. Mahaux, Jacques: Action de l'hormone thyroïdienne sur le métabolisme basal de lapins normaux et de lapins ayant présenté précédemment une période d'inversion d'action de l'hormone thyroïdienne, *Compt. rend. Soc. de biol.* **132**: 97-99, 1939.

5. Collip, J. B., and Anderson, E. M.: Production of Serum Inhibitory to the Thyrotropic Hormone, *Lancet* **1**: 76-78 (Jan. 13) 1934. Anderson, E. M., and Collip, J. B.: Preparation and Properties of an Antithyrotropic Substance, *ibid.* **1**: 784-786 (April 14) 1934; Studies on the Physiology of the Thyrotropic Hormone of the Anterior Pituitary, *J. Physiol.* **82**: 11-25 (Aug. 24) 1935.

6. Masay, F.: L'acromégalie expérimentale, *Bull. Soc. roy. d. sc. méd. et nat. de Bruxelles* **64**: 338-346, 1906.

7. (a) Eitel, Hermann, and Loeser, Arnold: Die Hemmung der Schilddrüsenaktivität durch Tierblut, *Klin. Wchnschr.* **13**: 1742-1744 (Dec. 8) 1934; Die antithyrotropische Schutzkraft des Blutes, *Arch. f. exper. Path. u. Pharmacol.* **177**: 737-751, 1935. (b) Oudet, P.: Propriétés antithyrotropiques du sérum d'animaux traités par la thyro-stimuline préhypophysaire, *Compt. rend. Soc. de biol.* **123**: 1177-1179, 1936.

8. Harington, C. R., and Rowlands, I. W.: Fractionation of Antithyrotropic and Antigonadotropic Sera, *Biochem. J.* **31**: 2049-2054 (Nov.) 1937.

9. Cope, C. L.: The Young Chick as Test for the Thyrotropic Hormone, *J. Physiol.* **94**: 358-364 (Dec. 14) 1938.

10. Billingsley, L. W.: O'Donovan, D. K., and Collip, J. B.: The Specific Metabolic Principle of the Pituitary, *Endocrinology* **24**: 63-68 (Jan.) 1939.

11. Eitel, Hermann, and Loeser, Arnold: Die Bedeutung der Schilddrüse für die antithyrotropische Schutzkraft des Blutes, *Arch. f. exper. Path. u. Pharmacol.* **179**: 430-437, 1935.

12. Rowlands, I. W., and Parkes, A. S.: Study of Anti-Thyrotropic Activity, *Proc. Roy. Soc., London, s. B* **120**: 114-125 (May 1) 1936.

13. Eichbaum, Franz, and Kindermann, Viktor: Untersuchungen über die antigenen Funktionen von Hormonpräparaten: thyrotropes Hypophysenvorderlappenhormon, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **89**: 498-511 (Dec. 31) 1936. Eichbaum, Franz; Kindermann, E.; Oestreicher, F., and Reiss, M.: Zur Frage der Unwirksamkeit des thyrotropen Wirkstoffes bei andauernder Zufuhr, *Endokrinologie* **18**: 375-378, 1937. Oudet, P.: Recherches sur les propriétés anti-thyrotropiques du sang d'animaux traités, durant une courte période, par un extrait purifié de préhypophyse, *Compt. rend. Soc. de biol.* **126**: 710-711, 1937.

14. Cope, C. L.: Effect of Antithyrotropic Serum on the Action of Human Thyrotropic Hormone, *Lancet* **1**: 888-890 (April 16) 1938.

15. Werner, S. C.: Prolonged Injection of a Thyrotropic Extract Without Development of Refractoriness, *Proc. Soc. Exper. Biol. & Med.* **34**: 390-392 (April) 1936; Antibody Nature of Refractoriness to Injections of Hypophyseal Extracts Containing Thyrotropic Hormone, *ibid.* **34**: 392-394 (April) 1936. Cutting, W. C.; Robson, G. B., and Emerson, Kendall, Jr.: Refractoriness from Pituitary Thyrotropic Extracts, *Endocrinology* **24**: 739-740 (May) 1939.

16. Mahaux, Jacques: Action du sérum de lapins à métabolisme abaissé par administration prolongée d'hormone thyroïdienne sur le métabolisme basal de lapins normaux, *Compt. rend. Soc. de biol.* **132**: 99-102, 1939.

17. Loeser, Arnold: Die Bedeutung der Hypophyse für die antithyrotropische Schutzkraft des Blutes, *Arch. f. exper. Path. u. Pharmacol.* **180**: 458-465, 1936.

18. Scowen, E. F., and Spence, A. W.: Effect of Antithyrotropic Serum on the Thyroid Gland of Guinea-Pigs Treated with Thyrotropic Hormone, *J. Physiol.* **86**: 109-116 (Jan. 15) 1936.

19. (a) Collip, J. B., and Anderson, E. M.: Studies on the Thyrotropic Hormone of the Anterior Pituitary, *J. A. M. A.* **104**: 965-969 (March 23) 1935. (b) Herold, Ludolf: Nachweis und Auswertung von anti-thyroidalen Schutzstoffen im Blute von Basedowkranken und Schwangeren, *Klin. Wchnschr.* **13**: 1242-1244 (Sept. 1) 1934. (c) Eitel, Hermann: Die antithyrotropische Schutzkraft des Blutes gesunder und kranker Menschen, *ibid.* **17**: 1465-1467 (Oct. 15) 1938. Scowen and Spence.<sup>18</sup>

20. Young, F. G.: Preparation of Antisera to Preparations of Prolactin Containing the Glycocytoprotic (Anti-Insulin) Factor of the Anterior Pituitary Gland, *Biochem. J.* **32**: 656-664 (April) 1938.

21. Spence, A. W., and Witts, L. J.: Substitution Therapy in Hypopituitarism, *Quart. J. Med.* **8**: 69-77 (Jan.) 1939.

tion.<sup>22</sup> Collip and Anderson,<sup>19a</sup> Loeser<sup>17</sup> and Gessler<sup>23</sup> all agree that it can be formed by hypophysectomized animals. It has been suggested that it cannot be formed by thyroidectomized animals (and even that it is identical with thyroxine<sup>21</sup>), but this has been denied.<sup>24</sup> Estrogens<sup>25</sup> may have some antithyrotropic activity, but this can hardly be relevant.

#### THE ANTIGONADOTROPIC SUBSTANCE

When chorionic gonadotropin (from human pregnancy urine or placenta) is administered for long periods to female rats, the weights of the ovaries increase at first but later decline to or below the normal level, as a refractory phase is entered;<sup>25</sup> a similar effect is observed when the ovaries are chronically stimulated by daily implantation of rat pituitary tissue.<sup>26</sup> In the refractory state the ovaries may be markedly atrophic and "wheel cells" may appear in the theca (a finding characteristic of complete absence of hypophysial stimuli), while typical "signet ring" castration cells appear in the anterior lobe of the pituitary.<sup>27</sup> The refractory ovaries are not exhausted and incapable of responding to any stimulus, for those which have become refractory to the influence of chorionic preparations still respond to hypophysial preparations<sup>28</sup> and vice versa.<sup>26</sup> The serum of animals with such refractory ovaries will prevent the usual response of immature female rats to appropriate gonadotropic stimulation.<sup>29</sup> Analogous phenomena are observed in male rats and in other species.

The question whether the antigonadotropic substance is an immune body, produced in response to the injection of foreign protein, or is to be regarded in some other light—for example, as a normal constituent of the organism—has been eagerly debated, and much of the discussion has centered on the problem of specificity, which in this case is exceedingly complex. One has to consider (1) species specificity, the comparison of extracts from the hypophyses (or other organs) of different species; (2) extract specificity, the comparison of extracts made from the same material by different procedures; (3) hormone specificity, the comparison of extracts having different ratios of follicle-stimulating

and luteinizing (interstitial cell-stimulating) activity, and (4) organ specificity—for example, the comparison of preparations from human pregnancy blood or serum with extracts from human hypophysis or menopausal urine (which has been little studied), or of preparations from the serum of pregnant mares with extracts from equine hypophysis.

Female rats which have become refractory to chorionic gonadotropin still respond to implants or extracts of animal hypophyses<sup>28</sup> or pregnant mare serum but not, it is claimed, to extracts from human hypophysis.<sup>30</sup> The serum of such rats is said to protect test animals against gonadotropic stimulation, not only that with chorionic gonadotropin but that with human hypophysial extracts<sup>31</sup> and even that with bovine hypophysial extracts;<sup>32</sup> it is more usually found, however, that preparations from animal pituitaries or pregnant mare serum are not inhibited.<sup>33</sup> Rowlands,<sup>34</sup> who carried out careful and extensive cross tests, concluded that human chorionic gonadotropin displayed species specificity but not organ specificity. It has been claimed that the serums of animals refractory to the gonadotropin of pregnant mare serum will confer resistance against gonadotropic preparations from the hypophyses of horses,<sup>35</sup> sheep or pigs<sup>36</sup> or from human pregnancy urine,<sup>37</sup> but this has been denied,<sup>38</sup> and Rowlands<sup>34</sup> concluded that both organ specificity and species specificity are displayed, only mare's serum being inhibited. Serums obtained by treatment with hypophysial extracts show little specificity;<sup>34</sup> they confer protection against extracts from other species<sup>39</sup> or pregnant mare serum,<sup>40</sup> though they may have little action against human chorionic gonadotropin.<sup>41</sup> Under some circumstances<sup>42</sup> it seems possible to obtain serums which inhibit the luteinizing rather than the follicle-stimulating hormone.<sup>43</sup>

Further evidence of a lack of specificity hard to reconcile with an immunologic interpretation may be found in observations that antigonadotropic serums not merely inhibit injected gonadotropic preparations but

30. Kabak, J.: Species-Specificity of the So-Called Anti-Hormones. *Bull. de biol. et de méd. expér. U. R. S. S.* 1: 342, 1936.

31. Brandt, Robert, and Goldhammer, Helene: Die Spezifität der gonadotropen Antiseren. *Ztschr. f. Immunitätsforsch. und exp. med.* 8: 79-90 (May 30) 1936. de Fremery, P.: Properties of the Gonadotropic Hormones of the Anterior Pituitary. *Acta endocrinol. (Copenh.)* 1: 133-135, 1937. Zondek, Bernhard, and Sulman, Felix: The Antigonadotropic Factor, Species Specificity and Organ Specificity. *Proc. Soc. Exper. Biol. & Med.* 36: 712-717 (June) 1937.

32. Gegerson, H. J.; Clark, A. R., and Kurzrok, Raphael: Studies on Gonadotropic Antihormones. *Proc. Soc. Exper. Biol. & Med.* 35: 193-195 (Oct.) 1936.

33. Fluhmann, C. F.: Species-Specificity in Production of Anti-Gonadotropic Substances. *Proc. Soc. Exper. Biol. & Med.* 32: 1595-1596 (June) 1935.

34. Rowlands, I. W.: Specificity of Antigonadotropic Sera. *Proc. Roy. Soc., London, s. B* 124: 503-521 (Jan. 14) 1938.

35. Simonnet, H., and Michel, E.: Recherches expérimentales sur la nature des antihormones. *Compt. rend. Soc. de biol.* 129: 918-921, 1938.

36. Thompson, K. W., and Cushing, Harvey: Inhibition of Action of Pituitary Hormones by Animal Sera. *Proc. Roy. Soc., London, s. B* 121: 501-517 (Jan. 1) 1937.

37. Guercio, Francesco, and Cazzola, Dino: Su alcune caratteristiche che permettono di distinguere gli antiormoni antigonadotropi dai comuni anticorpi. *Atti Accad. med. lombarda* 25: 1, 1939.

38. Gustus, E. L.; Meyer, R. K., and Dingle, J. H.: Relationship of Precipitin Titers to Gonadotropic Inhibitory Action of Monkey Sera. *Proc. Soc. Exper. Biol. & Med.* 33: 257-261 (Nov.) 1935.

39. Parkes, A. S., and Rowlands, I. W.: Inhibition of Ovulation in the Rabbit by Anti-Gonadotropic Serum. *J. Physiol.* 88: 305-311 (Dec. 11) 1936. Thompson and Cushing.

40. Collip, J. B.: Results of Further Experiments with the Anti-Maturity Hormone. *Canad. M. A. J.* 36: 199-200 (Feb.) 1937.

41. Collip, J. B., and Fluhmann, C. F.: Accoutumance aux hormones préhypophysaires et sérums protecteurs. *Rev. suisse de zool.* 44: 153, 1937.

42. W. S.: Selective Neutralization of the Luteinizing Extracts of Pituitary by Antisera. *Proc. Roy. Soc., London, s. B* 76-87 (Sept. 23) 1938; Rate of Appearance of Anti-Pituitary Glands. *J. Endocrinol.* 1: 172-176 (Sept.) 1939. Freud, J.: Notes on Refractoriness to the Action of Hormones. *Acta brev. Neerland.* 9: 161-163, 1939.

22. Loeser, Arnold, and Trikojus, V. M.: Untersuchungen über die Gewinnung antithyrotroper Wirkstoffe aus Blut. *Ber. d. naturforsch. Gesellsch. Freiburg-Br.* 35: 211, 1937.

23. Gessler, Carl: Activité antithyroïdienne de la folliculine; rôle de l'hypophyse. *Arch. internat. de pharmacodyn. et de thérap.* 55: 267-281 (March 31) 1937.

24. Oudet, P.: Rôle éventuel de la sécrétion thyroïdienne dans la mise en jeu des propriétés antithyroïdiantes du sérum d'animaux traités par la thyroestimine préhypophysaire. *Compt. rend. Soc. de biol.* 123: 1180-1181, 1936. Chou, C. H.: Antithyrotropic Effect of Serum of Normal and Thyroidectomized Rabbits. *Chinese J. Physiol.* 12: 155-162 (Sept. 15) 1937.

25. Zondek, Bernhard: Hormone des Ovariums und des Hypophysenvorderlappens. Berlin, Julius Springer, 1931. Collip, J. B.: Placental Hormones. *Internat. Clin.* 4: 51-70 (Dec.) 1932. McPhail, M. K.: Effect on Reproductive Organs of the Rat of Prolonged Treatment with Ovary-Stimulating Substances. *J. Physiol.* 80: 105-112 (Nov. 9) 1933.

26. Selye, Hans; Collip, J. B., and Thomson, D. L.: Loss of Sensitivity to the Gonadotropic Hormone of the Hypophysis. *Proc. Soc. Exper. Biol. & Med.* 31: 566 (Feb.) 1934.

27. Collip, J. B.; Selye, Hans, and Thomson, D. L.: Histological Changes in the Hypophysis Produced by Chronic Administration of Hypophysial Extracts. *Proc. Soc. Exper. Biol. & Med.* 31: 682-683 (March) 1934. Collip, J. B.; Selye, Hans, and Williamson, J. E.: Changes in the Hypophysis and the Ovaries of Rats Chronically Treated with an Anterior Pituitary Extract. *Endocrinology* 23: 279-284 (Sept.) 1938. Severinghaus, Aura E., and Thompson, K. W.: Cytological Changes Induced in Hypophysis by Prolonged Administration of Pituitary Extract. *Am. J. Path.* 15: 391-412 (July) 1939.

28. Selye, Hans; Collip, J. B., and Thomson, D. L.: Loss of Sensitivity to Anterior-Pituitary-Like Hormone of Pregnancy Urine. *Proc. Soc. Exper. Biol. & Med.* 31: 487-488 (Jan.) 1934.

29. Selye, Hans; Bachman, Carl; Thomson, D. L., and Collip, J. B.: Further Studies on Loss of Sensitivity to Anterior-Pituitary-Like Hormone of Pregnancy Urine. *Proc. Soc. Exper. Biol. & Med.* 31: 1113-1115 (June) 1934. Twombly, G. H., and Ferguson, R. S.: Protective Substances in Sera of Animals Injected with Anterior-Pituitary-Like Hormone of Teratoma Testis Urine. *ibid.* 32: 69-71 (Oct.) 1934. Bachman, Carl; Collip, J. B., and Selye, Hans: Anti-Gonadotropic Substances. *ibid.* 32: 544-547 (Dec.) 1934.

when administered alone prevent the action of the endogenous gonadotropic hormones and have effects comparable to those of hypophysectomy. Thus the antisera may cause ovarian atrophy and suppress estrus in the female rat,<sup>44</sup> prevent ovulation following mating in the rabbit,<sup>39</sup> interrupt pregnancy in the rabbit<sup>45</sup> and dog<sup>46</sup> and produce gonadal atrophy in male rats.<sup>45</sup> It will be noted also that antihormones have been produced by injection of sheep pituitary extract into sheep<sup>40</sup> or implantation of rat pituitaries into rats<sup>26</sup> (though difficulty has been encountered in repeating the latter experiment<sup>47</sup>), in which there is no question of foreign protein. Moreover, although complement-fixing antibodies and precipitins may appear in the serum of animals treated with preparations from urine, nearly all of the many students of this subject agree that there is no parallelism between the immunologic titer and the quantity of antigonadotropic substance physiologically determined, and that the former depends on contaminating proteins rather than on the gonadotropin itself.<sup>48</sup> If sera prepared by treatment with bovine pituitary extract are treated with bovine serum, the antiovine immune bodies are precipitated while the antigonadotropic activity remains.<sup>32</sup>

Other observations, however, favor an immunologic interpretation, or at least suggest that the antihormone is formed only under abnormal experimental conditions. Antigonadotropic activity has been ascribed to,<sup>49</sup> and denied<sup>50</sup> to, the serum of untreated human beings and animals, and was not found in human puerperal serum despite the high gonadotropic titer throughout pregnancy;<sup>51</sup> indeed, it is usually absent from the serum of patients long treated with preparations of chorionic gonadotropin,<sup>52</sup> though a positive result has recently been reported with pregnant mare serum.<sup>53</sup> Again when a castrate animal is linked with a normal one in parabiosis, the latter shows no sign of becoming

refractory to the gonadotropic hormone produced in excess by the former,<sup>54</sup> though it may be passively protected by transfer of serum from an animal made refractory by injections.<sup>55</sup> It is claimed, too, that antigonadotropic substance is produced in response to injections of chorionic gonadotropin which has been inactivated by heat or aging or ultraviolet irradiation,<sup>56</sup> or of extracts from male urine practically devoid of gonadotropic activity;<sup>57</sup> Zondek and co-workers,<sup>58</sup> however, have maintained that in all such preparations there remains a residue of gonadotropic potency and also that the neutralization of the injected gonadotropin by the antihormone follows quantitative or stoichiometric laws quite unlike those governing antigen-antibody reactions, on the one hand, or enzyme reactions, on the other;<sup>59</sup> hence Zondek has abandoned his earlier view that the antihormone is a specific hormone-destroying enzyme belonging to the class of Abderhalden's abwehrfermente.

The antigonadotropic substance is divided between the euglobulin and pseudoglobulin fractions of the serum<sup>6</sup> and can be purified by iso-electric precipitation.<sup>60</sup> It does not arise from the gonads, as it can be formed by castrate animals; it has been urged that it is produced by the reticuloendothelial system, like true antibodies, since its formation is inhibited by "blockage" and splenectomy;<sup>61</sup> it has also been urged that the pineal gland contains an antigonadotropic substance.<sup>62</sup> Certain anterior pituitary extracts when injected intraperitoneally diminish the effect of simultaneous subcutaneous injections of extracts containing the follicle-stimulating substance, and are said to contain an "antagonist," which may be identical with the luteinizing (interstitial cell-stimulating) factor but is almost certainly distinct from the antigonadotropic substance found in serum.

A curious and unexplained phenomenon which has been observed repeatedly is that, before antigonadotropic properties appear in the serum of a treated animal, there may be a phase during which the serum, far from inhibiting, augments the action of gonadotropic extract in a test animal.<sup>63</sup> It has been suggested that this "progonadotropic" effect represents the forma-

44. Collip.<sup>40</sup> Thompson and Cushing.<sup>20</sup>  
45. Rowlands, I. W.: Effect of Anti-Gonadotropic Serum on Reproductive Organs of the Normal Animal, *Proc. Roy. Soc., London*, S. B 121: 517-532 (Jan. 1) 1937.

46. Thompson, K. W.: Termination of Pregnancy of Dogs by Gonadotropic Antihormone, *Endocrinology* 24: 613-616 (May) 1939.

47. Katzman, P. A.; Wade, N. J., and Doisy, E. A.: Effects of Chronic Implantation of Rats with Pituitaries of the Same Species, *Endocrinology* 21: 1-7 (Jan.) 1937. Artemov, N. M.: Influence of Chronic Homoinjections of the Pituitary Body upon the Genital System of Female Rats, *Bull. de biol. et de méd. exper. U. R. S. S.* 3: 642-645, 1937.

48. Bachman, Carl: *Proc. Soc. Exper. Biol. and Med.* 1939. Franz, and Kindman.

Funktionen von Hormonpräparaten; gonadotropes Hypophysenvorderlappenhormon, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* 86: 284-299 (Nov. 13) 1935; 89: 230-238 (Nov. 3) 1936. Demanche, R.; Laroche, Guy, and Simonnet, H.: Etude critique de la réaction de fixation du complément appliquée à la recherche des antihormones dans le sang, *Compt. rend. Soc. de biol.* 125: 718-719, 1937. Guercio, Francesco, and Cazzola, Dino: Osservazioni sui rapporti tra siero antiorione e specificità zoologica, *Arch. di fisiol.* 39: 409, 1939. Meyer, R. K., and Wolfe, H. R.: Gonadotropic Inhibitory Substances and Precipitins in the Blood of Mammals, *Proc. Soc. Exper. Biol. and Med.* 1939.

49. J. Imm. 1939. van den Ende, M.: Precipitins, *J. Endocrinol.* 1: 156-171 (Sept.) 1939. tracts and Anaphylaxis in Vitro, *ibid.* 1: 356-363 (Nov.) 1939. Howell, K. M., and Soskin, Samuel: Antibody Response of Rabbits to Extracts of Human Pregnancy Urine and to Extracts of Normal Female Urine, *Endocrinology* 26: 577-580 (April) 1940. Gustus, Meyer and Dingle.<sup>23</sup> Brandt and Goldhammer.<sup>21</sup> Sulman.<sup>24</sup>

50. Collip and Anderson.<sup>19</sup> Brandt and Goldhammer.<sup>21</sup> Sulman.<sup>24</sup> Twombly.<sup>26</sup> Chen, Graham: Attempts to Produce Antigonadotropic Substance by the Use of Serum or Blood Extracts, *Chinese J. Physiol.* 11: 329-333 (March 1) 1937.

51. Fellows, M. D.: Antigonadotropic Hormone in Normal Human Blood Serum, *Endocrinology* 26: 369-376 (March) 1940.

52. Sulman, Felix: Does the Gonadotropic Hormone Induce Antibodies or Antihormones? *J. Exper. Med.* 65: 1-14 (Jan.) 1937.

53. Spence, A. W.; Scowen, E. F., and Rowlands, I. W.: Absence of Antigonadotropic Substances in the Blood Serum of Man Injected with Gonadotropic Extracts, *Brit. M. J.* 1: 66-67 (Jan. 8) 1938. Saphir, William; Howell, Katharine M., and Kunstadter, R. H.: Human Serum Response to Gonadotropic Hormone, *Endocrinology* 24: 182-186 (Feb.) 1939. Dorff, G. B.: Antihormone Studies in Boys Treated with Anterior Pituitary-Like Hormone, *ibid.* 22: 669-673 (June) 1938. Sulman.<sup>24</sup> Brandt and Goldhammer.<sup>21</sup>

54. Rowlands, I. W., and Spence, A. W.: Production of Antigonadotropic Activity in Man by Injection of Extract of Pregnant Mares' Serum, *Brit. M. J.* 2: 947-950 (Nov. 11) 1939.

54. Martins, T.: Sur la question des antihormones, *Compt. rend. Soc. de biol.* 119: 753-755, 1935. Du Shane, G. P.; Levine, W. T.; Pfeiffer, C. A., and Witschi, E.: Experimental Constant Oestrus and the Notion of Anti-Gonadotropic Hormones, *Proc. Soc. Exper. Biol. & Med.* 33: 339-345 (Dec.) 1935.

55. Kupperman, H. S.; Meyer, R. K., and Hertz, Roy: Effect of Antigonadotropic Sera upon Gonadotropic Secretion in Parabiotic Rats, *Endocrinology* 24: 115-118 (Jan.) 1939.

56. Twombly, G. H.: Studies of the Nature of Antigonadotropic Substances, *Endocrinology* 20: 311-317 (May) 1936.

57. de Fremery, P., and Scheygrond, B.: Inhibition of the Gonadotropic Activity of Pregnancy Urine Extract by the Serum of Rabbits Injected with an Extract of Male Urine, *Nature, London* 139: 1015-1016 (June 12) 1937.

58. Zondek, Bernhard; Sulman, Felix, and Hochman, Abraham: Relationship between Inactivated Prolan and Antiprolan, *Proc. Soc. Exper. Biol. & Med.* 39: 283-287 (Nov.) 1938.

59. Zondek, Bernhard; Sulman, Felix, and Hochman, Abraham: Quantitative Aspects of the Prolan-Antiprolan Reaction, *Proc. Soc. Exper. Biol. & Med.* 40: 96-98 (Jan.) 1939.

60. Zondek, Bernhard; Sulman, Felix, and Hochman, Abraham: The Preparation of Concentrated Antigonadotropic Factor (Antiprolan), *Biochem. J.* 32: 1891-1896 (Nov.) 1938.

61. Gordon, A. S.; Kleinberg, William, and Charipper, H. A.: Relation of Prolan to Refractoriness Developed in Response to Refractoriness, *Proc. Soc. Exper. Biol. & Med.* 36: 484-486 (June) 1938.

62. Engel, P.: Zirbeldrüse und gonadotropes Hormon, *Ztschr. f. d. ges. exper. Med.* 94: 333-345, 1934; Weitere Untersuchungen über die biologischen und chemischen Eigenschaften des antigonadotropen Hormons der Zirbeldrüse, *ibid.* 96: 328-336, 1935.

63. Katzman, Wade and Doisy.<sup>45</sup> Collip.<sup>40</sup> Thompson, K. W.: Augmentary Factor in Animal Sera After Injections of Pituitary Extract, *Proc. Soc. Exper. Biol. & Med.* 35: 640-644 (Jan.) 1937. Rowlands, I. W.: Pro-Gonadotropic Sera, *Proc. Roy. Soc., London*, S. B 124: 492-503 (Jan. 14) 1938; Further Observations on Pro-Gonadotropic and Antihypophyseal Activity of Antisera to Extracts of the Anterior Pituitary Gland, *J. Endocrinol.* 1: 177-183 (Sept.) 1939. Katzman, P. A.; Wade, N. J., and Doisy, E. A.: Progonadotropic Sera of Animals Treated with Hypophyseal Extracts, *Endocrinology* 25: 554-567 (Oct.) 1939.

tion of an antihormone to the aforementioned "pituitary antagonist," but there is little direct evidence for this interpretation. The progonadotropic substance is found in the globulin fraction of serum and is active in hypophysectomized as well as in normal test animals and in males as well as in females.

#### ACQUIRED RESISTANCE TO OTHER PRINCIPLES

Animals become refractory to the action of prolactin, and an inhibitory substance may be demonstrated in their serum.<sup>64</sup> The diabetogenic effect of fresh anterior pituitary extracts in normal dogs does not persist in long treatment except with enormous doses; this might be due to increased production of insulin, but a similar phenomenon has been observed in depancreatized animals.<sup>65</sup> The glycostatic action on muscle glycogen cannot be maintained indefinitely, nor the growth-promoting action of purified extracts, nor the ketogenic effect; in the last case, there is some evidence that an antihormone is formed.<sup>66</sup> Glycotropic (anti-insulin) activity can, however, be maintained without refractoriness for long periods. The "tachyphylaxis" observed with pitressin need not be considered here.

According to Hartman<sup>67</sup> adrenal cortical extracts may be regarded as consisting of two fractions, one of which is life maintaining while the other ("Na factor") causes sodium retention in normal animals. Intravenous or intraperitoneal (but not subcutaneous) injections of the latter gradually lose in efficacy, but the refractory state produced yields to similar extracts from adrenals of another species. The serum of refractory animals, or its pseudoglobulin fraction, confers resistance against the adrenal extract originally used in fresh test animals (dogs). Such resistance can develop in adrenalectomized animals, and is not elicited by chemically pure preparations, such as corticosterone.

The practical importance of finding means to control metabolism in hyperthyroidism has led to many studies of "antithyroid" substances, not all of which can be discussed here. The "antithyroidin" of Möbius<sup>68</sup> was obtained from the blood of thyroidectomized sheep, and was followed by the "catechin" of Blum<sup>69</sup> from normal bloods, apparently identical with the preparation marketed as "tyronorman," which has been widely if not always critically used in the treatment of exophthalmic goiter<sup>70</sup> and which is said to possess antithyrotropic as well as antithyroid properties<sup>71</sup> but appears to be associated with the fat-soluble fractions of the blood rather than with the proteins. True anti-

bodies appear in immunization with thyroglobulin but do not lead to refractoriness to the metabolic action of this substance.<sup>72</sup>

Parathyroid preparations soon lose their hypercalcemic activity when continuously administered, but there is no reason to believe that an antihormone is produced. Insulin may be given to diabetic patients for years without development of resistance, yet the phenomenon is sometimes encountered, and in one case the blood seemed to destroy or inhibit insulin;<sup>73</sup> the name "anti-insulin" has been used at various times, both for hyperglycemic factors in crude pancreatic extracts and for the glycotropic factor of the anterior lobe of the pituitary. With chemically pure estrogens, androgens, progesterone or epinephrine there is in general no sign of acquired resistance to the ordinary physiologic effects, though animals may display ability to adapt themselves to the damaging effects of excessive doses;<sup>74</sup> one is not justified in speaking of specific antihormones in these cases. Attempts to produce complement-fixing antibodies by using estrogens and androgens as haptens with pig serum as a carrier have succeeded, but the physiologic actions of these substances are not inhibited.<sup>75</sup>

## Council on Physical Therapy

THE COUNCIL ON PHYSICAL THERAPY HAS AUTHORIZED PUBLICATION OF THE FOLLOWING ARTICLE.

THE COUNCIL WISHES TO EXPRESS ITS APPRECIATION TO DR. LAURISTON S. TAYLOR FOR THE PREPARATION OF THIS ARTICLE AND TO THE CONSULTANTS ON ROENTGEN RAYS FOR THEIR ASSISTANCE. THE CONSULTANTS ON ROENTGEN RAYS ARE DRs. A. U. DESJARDINS, CHAIRMAN, WILLIAM E. CHAMBERLAIN, A. C. CHRISTIE, E. C. ERNST, GIOACCHINO FAILLA, F. M. HODGES, J. T. MURPHY, R. R. NEWELL, E. P. PENDERGRASS, U. V. PORTMANN, L. S. TAYLOR AND J. L. WEATHERWAX.

HOWARD A. CARTER, Secretary.

### X-RAY PROTECTION

LAURISTON S. TAYLOR, PH.D.

WASHINGTON, D. C.

Proposals covering the broader aspects of x-ray and radium protection were adopted by the International Congress of Radiology in 1928, 1931, 1934 and 1937. These have formed a basis of more detailed recommendations by the National Advisory Committee on X-Ray and Radium Protection composed of representatives of the various radiologic and medical societies and the x-ray equipment manufacturers. However, certain types of questions in this matter frequently confront the physician and consequently it may be of value to discuss briefly a few of them.

#### SHIELDING FROM DIRECT RADIATION

*Complete X-Ray Shielding.*—In the deep and superficial therapy rooms it is most desirable in general that the nurse or technician be completely isolated from the

64. Young,<sup>59</sup> Strangeways, W. I.: Precipitin Tests and Anti-Prolactin Serum, *J. Physiol.* **93**:47P-48P (July 2) 1938. Rowlands, I. W., and Young, F. G.: Capacity of Pituitary Preparations Containing the Thyrotrophic Hormone to Induce the Formation of Antisera, *ibid.* **95**:410-419 (April 14) 1939. Bischoff, H. W., and Lyons, W. R.: Immunologic Investigation of Hypophyseal Mammotropic Preparations, *Endocrinology* **25**:17-27 (July 1) 1939.

65. Collip, J. B.: Some Recent Advances in the Physiology of the Anterior Pituitary, *J. Mt. Sinai Hosp.* **1**:28-71 (May-June) 1934. Dohlan, F. C., and Lukens, F. D. W.: Antihormone Effects in Pancreatic Diabetes, *Proc. Soc. Exper. Biol. & Med.* **42**:167-171 (Oct.) 1939.

66. Black, P. T.; Collip, J. B., and Thomson, D. L.: Effect of Anterior Pituitary Extracts on Acetone Body Excretion in the Rat, *J. Physiol.* **82**:385-391 (Oct. 17) 1934.

67. Hartman, F. A.; Lewis, L. A., and Gabriel, J. E.: Further Studies on the Refractory State Developed Following Repeated Injections of Adrenal Extract, *Endocrinology* **26**:879-885 (May) 1940.

68. Möbius, P. J.: Die Basedowsche Krankheit, Vienna, A. Hölder, 1906.

69. Blum, F.: Ueber die antithyreoidalen Eigenschaften des Blutes und das zugrundeliegende Catechin, *Schweiz. med. Wchnschr.* **63**:777-781 (Aug. 12) 1933.

70. Herzfeld, Ernst, and Frieder, Alexander: Ueber das Catechin (Hemmungstoff) der Schilddrüse und dessen therapeutische Verwendung bei Morbus Basedow, *Deutsche med. Wchnschr.* **59**:84-86 (Jan. 20) 1933.

71. Schneider, E., and Widmann, E.: Die Wirkung des Tyronormans, *Deutsche Ztschr. f. Ch.* **211**:1-11 (1933). Bach, S., and Pick, E. P.: Ueber die Wirkung des Tyronormans, *Wiener klin. Wchnschr.* **50**:1-11 (May 22) 1937. *Herold*,<sup>10</sup>

72. Hektoen, Ludvig, and Schulhof, Kamil: Precipitin Reaction of Thyroglobulin, *J. A. M. A.* **80**:386-387 (Feb. 10) 1923. Hektoen, Ludvig; Fox, H., and Schulhof, Kamil: Specificity in the Precipitin Reaction of Thyroglobulin, *J. Infect. Dis.* **40**:641-646 (June) 1927. Schulhof, Kamil: Effect of Antithyroglobulin Serum on the Physiological Action of Thyroglobulin, *Am. J. Physiol.* **93**:175-177 (May) 1930. Rosen, S. H., and Marine, David: Immunity to Iodothyroglobulin Does Not Affect Its Physiological Action, *ibid.* **120**:121-123 (Sept.) 1937.

73. Banting, F. G.; Franks, W. R., and Gairns, S.: Anti-Insulin Activity of Serum of Insulin-Treated Patient, *Am. J. Psychiat.* **93**:562-564 (Nov.) 1938.

74. Selye, Hans: Studies on Adaptation, *Endocrinology* **21**:169-183 (March) 1937.

75. Brandt, Robert, and Goldhammer, Helene: Antikörper gegen lipide Hormone, *Klin. Wchnschr.* **17**:1875-1877 (Dec. 19) 1936.

patient, since that affords complete protection from both direct and scattered radiation. To realize this practically, the treatment room should be constructed of some completely protective material, and observation by the nurse should be only through amply protecting lead glass.

Three types of such room construction are possible: (1) metallic lead walls, (2) protective plaster walls, such as barium plaster, and (3) poured concrete or solid concrete block wall. In all cases, considerable care must be given to the details of construction. Each of the three types of protective material has its own place depending on such factors as the operating voltage and the intensity of the radiation against which protection is sought.

In general the barium plaster walls find best application in the diagnostic and superficial therapy voltage range; lead, in the superficial therapy and moderate voltage deep therapy range (up to 220 kilovolts), and concrete for all higher voltage radiations. When one is using either plaster or concrete it should be borne in mind that for the same degree of protection one must use a weight of material per square foot which is usually considerably greater than pure lead. The efficiency of concrete as a protective material increases rapidly with thickness and increasing excitation voltages.

*Internationally Adopted Thickness for Lead Protection*

X-Rays Generated by Peak Voltages Not in Excess of Kv.	Minimum Equiva- lent Thickness of Lead, Mm.
75	1.0
100	1.5
125	2.0
150	2.5
175	3.0
200	4.0
225	5.0
300	9.0
400	15.0
500	22.0
600	34.0

The lead protection thicknesses adopted internationally are given in the accompanying table. The thicknesses given in this table will reduce a beam having a dosage rate of 6 roentgens per minute at 100 cm. from the target to the safe tolerance level just behind the barrier. It is obvious, therefore, that for higher or lower dosage rates (measured at 1 meter) or for greater distances from a permanently located x-ray tube the necessary lead protection may increase or decrease depending on conditions. Thus a spacious therapy room will not require as much protection per square foot as a small and cramped room. These factors have been considered in detail in other publications.

*Partial X-Ray Shielding.*—The next type of shielding is one that divides the protection into two classes: first, that which protects from direct radiation from the tube and, second, that which protects from the scattered radiation from the patient and surrounding objects.

It must be clearly understood, however, that increase in protection from one source must keep pace with increase in protection from the other. It is insufficient to provide perfect protection from direct radiation while neglecting largely the scattered radiation. The two degrees of protection should be so adjusted that the potential danger to the patient is about equal. At present the customary protection from scattered radiation is much less effective than from the direct radiation from the tube.

Although still used, lead-glass tube bowls are obsolete; their use is definitely dangerous and should be discouraged.

For therapeutic x-ray tubes, the surrounding shield should be sufficient to reduce the dosage rate of the undesired radiation to a level not exceeding 1 per cent, and preferably less, of that of the main beam when using the heaviest filtration. For diagnostic x-ray tubes the surrounding shield should reduce the radiation as measured at the position of the radiologist to a level at least as low as the dosage rate at the same point due to radiation scattered from the patient's body. It is obviously difficult to provide a general formula for such protection because of the wide variety of conditions encountered clinically.

There are many definite advantages to the metallic tube enclosures now commonly used. The electrical protection is nearly perfect when the shield is grounded. Also it is easy and desirable to cover the treatment window with a permanent aluminum or copper filter and a layer of asbestos. The physician is thereby first assured of some protection against the soft rays; second, in case the target should melt off or the tube break, the possibility of any hot parts falling on the patient is decreased; third, if, when one is using a water-cooled tube, the water connection leaks or breaks there is slight possibility of a high tension short circuit occurring to the patient.

Much can be said at this time in favor of the completely oil immersed x-ray tube for high voltages, and its development promises to be one of the most important in the improvement of x-ray technic. When the tube and transformer are in the same grounded case or connected by shielded cables, the electrical hazard is appreciably lessened. Such a unit is also adaptable to a satisfactory x-ray shielding.

#### PROTECTION FROM SCATTERED RADIATION

Up to the present too little attention has been paid to scattered radiation and it must be emphasized that one must not overprotect from direct while neglecting even in part the scattered rays. Operators should frequently inspect the equipment to be certain that no part of the protection has become accidentally displaced. In diagnostic work the patient needs no special protection from direct or scattered radiation, since the exposures are short and the intervals between such exposures long.

In therapy, the protection of a patient is important but is frequently neglected. Its importance increases for patients having frequent and long treatments. The treatment part of the body should be sharply defined and the remainder of the body carefully covered with sufficient lead rubber in cases in which the tube is an open bowl or otherwise poorly protected. If some part of the patient's body comes much closer to the target than the part which is being treated, the protection afforded by the shielded enclosure may not be sufficient. For cases in which the beam is sharply defined, such as from a large tube shield close to the patient, little or no extra covering for the patient is necessary.

When a patient lies on a metal table there will be a certain amount of secondary radiation scattered back to the patient from the table. This of course applies to all material and air in the direct beam or in fact near the patient. While in a great many cases this can be neglected, there are times when it must certainly be considered.

It cannot be overemphasized that the operator should remain outside the treatment room at all times when the tube is in operation. The controls must be conveniently located at a point outside the room or in a booth, either of which affords complete protection. Particular care must be given to the lead glass window to insure that it has a high enough protective coefficient. This is neglected in too many hospitals. In addition the window should afford a good view of the patient and high tension meters at the same time.

*Protection in Roentgenoscopy and Roentgenography.*—The danger from roentgen radiation is probably greater to the physician in roentgenoscopy and roentgenography than from any other source. Roentgenoscopic and roentgenographic apparatus is also used to a much greater extent than any other type and evidently till quite recently it has received the least attention from the point of view of protection. As already indicated, the danger is to the physician and not to the patient. Also the greatest source of this danger is from the scattered radiation and not the direct, as the latter is usually limited.

I will now assume that the tube is properly shielded in some way that has been outlined so that only a limited beam of direct radiation strikes the patient. By the use of adjustable diaphragms the field should be set at such a size as to be entirely included on the fluorescent screen. Unfortunately this has been considered the best protection or all that was necessary. However, actual observation with a hand roentgenoscope shows a large amount of scattered radiation on all sides of the screen of the patient and in the usual positions of the physician.

Measurements of scattered radiation around screening stands have been made by means of ionization chambers. In many cases the dose at the normal position of the physician has greatly exceeded the "tolerance dose." Curves have been plotted showing this distribution and its correction by the addition of proper screens.

Several direct remedies may be applied and developed to the point at which the further increase in safety is inconsistent with construction and general adaptability. There is no sharp line of demarcation for this, and the final solution can be worked out only by the roentgenologist and the manufacturer together.

First, the screen itself should be effectively backed with a lead glass of which the protective coefficient is to be determined by the voltage used.

Next, it is desirable that the fluorescent screen have thin sheet lead wings which overlap the glass and extend several inches to each side and top. Beneath the glass, and again overlapping, should hang some form of apron, preferably of lead rubber, so supported that the roentgenologist can reach the patient with his hands when necessary. This would give the roentgenologist good protection under all conditions. The increase in weight can be counterbalanced so as to permit freedom of motion. All the protection described applies principally to radiation scattered from the patient, air and surrounding objects.

In the case of horizontal screening and roentgenography, similar precautions should be taken when possible with regard to the fluorescent screen. Good protection is afforded the operator with such equipment by extending a lead shield of proper thickness along the side of and overlapping the patient and tube as far as practicable. If the shield is so mounted as

to move with the tube, it need be only from  $2\frac{1}{2}$  to 3 feet wide; otherwise it should extend the length of the table.

*Body Protection.*—The roentgenologist must at times use certain special forms of body protection. In general, however, the permanent protection should be sufficient so that he need only use protecting gloves and aprons. The use of goggles and the like in a poorly protected room gives a false sense of security and may lead to carelessness and thus to injury.

For adequate protection, gloves and aprons should have a lead equivalent of 0.5 mm. The rubber should be soft, pliable and kept free from cracks. White cotton gloves worn under the lead rubber gloves will make the lead rubber gloves last longer. The requirements for such protection have been discussed sufficiently in the proposals adopted by the second International Congress. It need only be emphasized that in the use of gloves and aprons the busy roentgenologist must use great care and not expect too much of them.

By means of so crude a device as a hand roentgenoscope, a roentgenologist can obtain quickly and readily some measure of the scattered radiation in his rooms. If he first accustoms his eyes to complete darkness for ten minutes and then is able to perceive fluorescence on the screen, he should take some immediate measure to shut off the leakage. In the same way he can examine his other protective materials such as glass and rubber. A film test, while not very accurate, can indicate to the radiologist the exposure to which he is subjected in the course of a day or a week. He should make a habit of examining in the same way all new protective materials which come into his use, as well as those which are subject to change in service, and not rely merely on the statements of the salesman; faulty material is always a possibility.

#### PROTECTIVE MATERIALS

Lead, when used in proper thickness, affords ample x-ray protection and calls for no further discussion.

Lead glass or lead-barium glass can be made in this country of uniform density and up to 60 per cent lead and 15 per cent barium without giving too much color. Its manufacture, however, is so expensive and the demand limited, that it is not handled by most glass dealers. Domestic lead glass has a protective coefficient as high as 0.30 (most imported glasses are relatively poor). This means that for an equivalent lead thickness of say one-eighth inch the lead glass must be slightly over three-eighths inch thick. This can be secured in one plate or by adding two or more plates to give the required thickness. The efficiency is in no way affected by the laminations.

Lead rubber can readily be made with a high lead content but this is not ordinarily done. When it is supplied with sufficient lead, and is pliable and free from cracks, it affords good protection. Care and judgment in its use must be observed, however.

Protective plasters must be mixed with great care in order to insure a uniform texture. Moreover, it is not easy to know just when a sufficient mixing has been given. Next it must be laid on a specially and carefully installed metal lath and allowed to set under temperature conditions which are preferably quite constant.

An undesirable feature of barium sulfate plaster is its wide variation of opacity with voltage. In general there is a maximum x-ray opacity at about 110 kilovolts which falls off to less than one half at 200 kilovolts for thicker walls. Thus for a plaster protection at 200 kilo-



volts the thickness will be double that at 100 kilovolts for the same percentage protection. The opacity is approximately proportional to the thickness of material at lower voltages but the relation is not so simple at 200 kilovolts. Properly installed barium plaster walls afford a satisfactory protective barrier up to at least 110 kilovolts.

The use of concrete or concrete block requires the same care in installation as for that of barium plaster. In general it is inefficient in thickness of less than 4 inches. Its greatest advantages appear in thicknesses over 6 inches and for voltages above 200 kilovolts. It has the important advantage of providing structural value for a building.

Lead sheets embedded in cinder blocks are now available and provide a satisfactory means of installing pure lead protection.

#### THE TOLERANCE DOSE

By the so-called "tolerance dose" is meant the amount of x-ray energy that a person may receive continuously or at repeated intervals without suffering any damage to the blood or reproductive organs. This can be expressed in terms of roentgens of radiation or in terms of an erythema dose. The actual values of this dose should be stipulated by the radiologist and not the physicist. It remains for the latter to measure it within certain limits and to devise means for reducing it when necessary. Obviously, the determination of this tolerance dose is difficult and at best uncertain. The biologic factor differs too greatly among individuals to permit the use of a sharply defined tolerance. To be well beyond the danger limit one must apply a generous factor of safety to the result of any physical measurements. Kaye has summed up the tolerance doses as estimated by five investigators and from these data finds that a person may receive without injury up to one-fiftieth roentgen daily. In each case a generous factor of safety has been allowed. The fact that this figure includes a large safety factor makes it unnecessary to stipulate the quality of the radiation or to state whether the whole body is exposed or only a portion of it.

The determination of the tolerance dose can be done only empirically. A number of hospitals are first chosen as being representative. In each, every worker is carefully examined for any physical damage to blood or tissues. Where they are found to be sound, a careful record of their day is made to determine their exposure to radiation. Next the intensity of the radiation is measured with a sensitive calibrated ionization dosage meter in terms of roentgens. Dividing the number of roentgens by the number of working minutes per day gives the dose in roentgens per minute. This can be converted into any desired unit for convenience.

#### SOME ELECTRICAL SAFEGUARDS

By far the most important electrical precaution is complete inaccessibility of all high tension leads. This applies not alone to the permanent aerial system but especially to the flexible conductors from the rheophores to the tube terminals. These leads are too commonly within easy reach of patient or doctor and many fatal accidents have been due to an excited patient rising on the table and touching the leads. With the recent improvements in apparatus this danger can be eliminated and every effort should be made to abolish exposed leads entirely.

It is of great importance that certain parts of the equipment be permanently connected to earth. Fre-

quent inspection should be made to ascertain that these connections are good. Whenever possible, the center point or end of the secondary should be effectively grounded. The non-current carrying parts of control panels, timing switches and so on should also be well grounded. When a milliammeter is used in the grounded side of the high tension circuit it should be shunted by a spark gap set at a distance of 1 or 2 thousandths of an inch. This can be easily done by short-circuiting the meter with two overlapping flat metal strips and then separating the strips with a piece of tissue or cigaret paper. This protects the meter from surges.

Insulating floor coverings are always desirable and are a necessity on concrete floors where the older exposed tube leads are used. Very good grades of rubber compound flooring or mats are made which will stand a breakdown voltage of more than 100 kilovolts through the body of the material. It should be laid preferably in strips as wide as possible so that a discharge cannot take place along the surface to an edge or crack. It should be installed carefully so as to avoid cracking or straining, and the edges should be from 1½ to 2 feet from the foot position of the operator when possible. When it is being cleaned, acid or strong soapy solutions should not be used. Wiping should be done only with a damp rag and moisture should be kept from under the edges; it should be dried thoroughly before using. When in addition x-ray protection is desired for a room beneath, a lead rubber flooring can be used effectively to serve both purposes. A break in the continuity of the floor covering resulting, for instance, from the dropping of a heavy object with sharp corners would nullify all these conditions.

In some forms of apparatus the main transformer is easily accessible and the high tension is conducted away through insulating tubing. Where such leads are also accessible they should be covered with a carefully grounded metallic sheathing. This minimizes danger from shock in case the insulation breaks down.

In diagnostic equipment one of two types of switch should be used in the transformer primary circuit, namely either a hand or a foot switch so constructed that the circuit is instantly broken when the pressure is relieved; or a time switch which automatically opens the circuit at the end of a set interval. Wherever possible two switches should be used in series to minimize the danger of accidental closing of the circuit.

In the use of insulated water-cooling systems when the tube is placed at a high potential every precaution must be made to prevent leakage of water. In particular any leakage must be prevented from striking the patient, as it might cause a short circuit of the high tension. This has been discussed in connection with the lead tube shield.

Much can be said for the development of completely insulated equipment and especial credit is due the manufacturer for his efforts in developing it. One of the most important developments is the completely oil-immersed units in which tube and transformer are in a common metal tank, air sealed and effectively grounded. The electrical hazard from high voltage shock in the better types vanishes. Such units are now being manufactured up to 400 kilovolts.

It is recognized that this discussion is far from complete, but it is hoped that it will serve as a guide in examining some of the safety aspects of x-ray equipment.

But, however safe x-ray equipment is made, it is a dangerous and lethal tool in the hands of the ignorant,

careless or inexperienced operator. It should be used only by qualified radiologists and technicians. The manufacturer has performed an admirable job in working out all phases of the safety problem; most companies make only reasonably safe equipment and cannot be held liable for the inadvised use of their product. Education and the restriction of sales only to qualified people will probably go furthest in minimizing the hazard of x-ray equipment.

THE COUNCIL ON PHYSICAL THERAPY HAS AUTHORIZED PUBLICATION OF THE FOLLOWING REPORTS.

HOWARD A. CARTER, Secretary.

### LIEBEL-FLARSHEIM DUAL WAVE SW-550, ACCEPTABLE

Manufacturer: The Liebel-Flarsheim Company, Cincinnati.

The Dual Wave SW-550 is recommended for medical and minor surgical diathermy. The unit is housed in a metal floor model cabinet. According to the firm, the Model SW-550 provides circuits for generating two wavelengths—one wavelength in the ultra-short wave range (approximately 8 meters), the other in the short wave range (approximately 24 meters).

The short wave circuit (24 meters) and the ultra-short wave circuit (8 meters) are of the tuned-plate, tuned-grid type. With both circuits the patient circuit is inductively coupled to the oscillator; a variable condenser in the patient circuit provides for resonance with the oscillator.

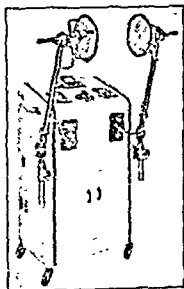
This unit employs two rectifier tubes type 966 and two oscillator tubes type WL-468. The WL-468 tubes carry the following manufacturer's rating:

A. C. (RMS) plate volt.....	2,500
D. C. plate milliamperes.....	200
Plate output watts (approximately).....	400

Physical tests performed in the Council laboratory disclosed that the apparatus has an input of 1,290 watts and an output of 500 watts by the lamp load method using the treatment drum, and one turn as load pick up. After the unit had been operating for two hours the final temperature of the transformer was found to be 95 F., which is within the limits of safety prescribed by the Council.

The net weight of the unit, complete with standard accessories, is 196 pounds; the shipping weight is 303 pounds.

The inductance cable and the flat and curved treatment drums operate on short wave (24 meters) circuit. The air-spaced plates, pads, cuffs and official electrodes operate on ultra-short wave (8 meters) circuit. The proper wavelength is automatically delivered to the respective electrode when the leads are plugged in. Applicators are said to be protected against overload and possible damage by a power regulator tube and circuit in the output circuit.



Liebel-Flarsheim Dual  
Wave SW-550.

The tubes and circuit are protected by a device (the Protect-A-Tube) which automatically reduces the power and sounds a warning signal when some unusual condition threatens an overload. A line filter is incorporated in the circuit and special precautions are said to have been taken by the manufacturer to balance the circuit in order to minimize radio interference.

Evidence as to the heating capabilities of the unit were submitted by the firm and confirmed by the Council's clinical investigation. The data are as follows:

#### INDUCTANCE CABLE (SHORT WAVE)

Technic: Four turns of the inductance cable were wrapped around the thigh with approximately 1 inch of turkish toweling beneath for spacing. Two turns were taken high up on the thigh; approximately 4 inches of spacing was allowed for inserting the thermocouple, and two more turns were taken below the incision.

Average temperatures of six tests:  
Deep muscle: initial, 98.5 F.; final, 107.7 F.

#### FLAT TREATMENT DRUM (SHORT WAVE)

Technic: The treatment drum was applied over the thigh, as close to the skin and as nearly over the point where the temperatures were read as the thermocouples would permit.

Average temperatures of six tests:  
Initial, 99.0 F.; final, 105.4 F.

#### CURVED TREATMENT DRUM (SHORT WAVE)

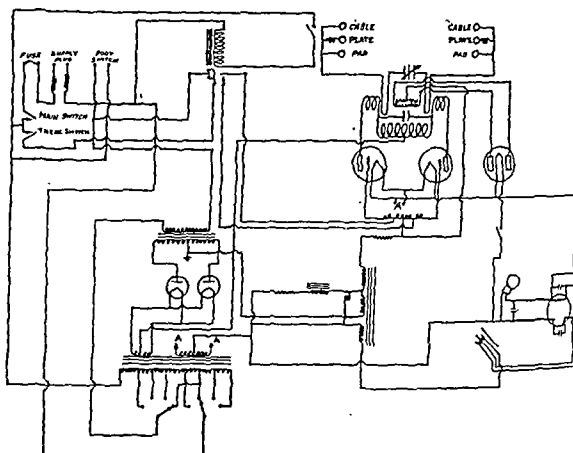
Technic: The curved treatment drum was applied over the thigh, as close to the skin and as nearly over the point where the temperatures were read as the thermocouples would permit.

Average temperatures of six tests:  
Initial, 98.8 F.; final, 105.4 F.

#### SPACED PLATE (ULTRA-SHORT WAVE)

Technic: Two disks, one 5½ inches in diameter and one 9½ inches in diameter, were applied in a plane to the anterior portion of the thigh and curved so that each portion of the plate was approximately the same distance from the skin surface. The proximal edges of the disks were 2 to 2½ inches apart, at the center of which space the thermocouple was inserted. Both disks were spaced approximately 1 inch from the patient's skin.

Average temperatures of six tests:  
Initial, 98.8 F.; final, 107.3 F.



Schematic diagram of circuit.

#### CUFFS (ULTRA-SHORT WAVE)

Technic: Two ultra-short wave cuff electrodes with approximately 1¼ inch turkish towel spacing were wrapped around the thigh with approximately 2½ inches space between the proximal edges. The thermocouples were inserted at the midpoint.

Average temperatures of six tests:  
Initial, 98.4 F.; final, 106.6 F.

#### PAD (ULTRA-SHORT WAVE)

Technic: Two ultra-short wave pad electrodes 6 by 8½ inches were spaced approximately 1½ inches with turkish toweling and curved to fit the contour of the thigh. Approximately 2 inches was left between the proximal edges at the center of which space the thermocouples were inserted.

Average temperatures of six tests:  
Initial, 97.9 F.; final, 105.7 F.

The following six tests show the results with use of an official electrode in connection with the ultra-short wave circuit of the Model SW-550.

Time	Temperature	Time	Temperature	Time	Temperature
5	104	5	104	5	105
10	109	10	106	10	108
15	110	15	111	15	109
20	110	20	110	20	110
5	105	5	105	5	104
10	107	10	108	10	106
15	110	15	109	15	109
20	111	20	110	20	111

In all cases the Chapman electrode was used and was specially drilled so that a thermometer could be passed through and actually come in contact with the cervical tissue.

The electrode was connected to the pad terminal on the apparatus (ultra-short wave) and a special lead incorporating a condenser was used for tuning this application. For a return path the large air-spaced plate was connected to the opposite

spaced-plate terminal and the plate was positioned at approximately 4 inches above the abdomen.

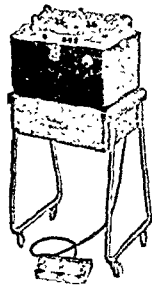
The Council voted to accept the Liebel-Flarsheim Dual Wave SW-550 for inclusion on its list of accepted devices.

### BIRTCHER MODEL 799 ELECTRO-SURGICAL UNIT ACCEPTABLE

Manufacturer: The Birtcher Corporation, 5087 Huntington Drive, North, Los Angeles, Calif.

The Birtcher Model 799 Electro-Surgical Unit is said by the manufacturer to be designed so that it can be used for all major and minor technics of electrosurgery. The unit is provided with a tube circuit for cutting and a spark gap circuit for coagulation, and the manner in which it is designed permits simultaneous use of the two circuits.

The spark gap circuit, indicated on the operating panel by a red pilot light and red dial, is located on the left hand side of the instrument, and current for this circuit is supplied by depressing the red part of the triple pedal foot switch. On the right hand side is located the tube cutting circuit, indicated by a green pilot light and green dial on the operation panel; depressing the green part of the foot switch supplies current for this circuit. Depressing the center pedal makes it possible for the operator to mix or blend the currents. The color distinction which is used provides a visual means of distinguishing between the two circuits. An auditory distinction is also employed; the spark gap circuit, when in operation, makes a "sizzling" sound, and the tube cutting circuit a radio tone sound.



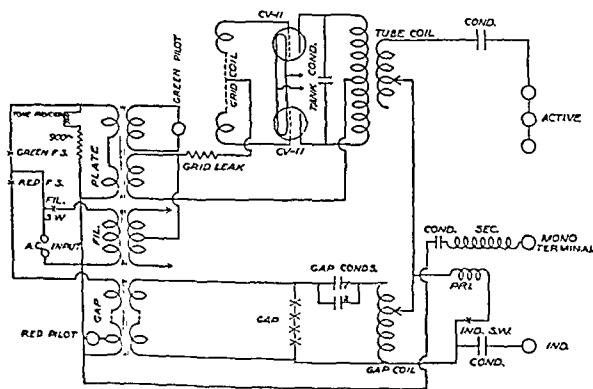
Birtcher, Model 799 Electro-Surgical Unit.

Standard equipment with the Birtcher Model 799 Electro-Surgical Unit includes dual footswitch, one line cord, one No. 795 Electro-Surgical set including five assorted loops and blades, one metal indifferent electrode with connection cord and two chromium plated steel rods for insertion in the control dials of the unit. The unit uses type CV-11 power tubes.

A report concerning the radio interference caused by the unit was submitted by the firm. It pointed out that at a distance of 1,500 feet no interference could be detected in the ultra short wave band or in the broadcast band. As the receiver used was an extremely sensitive one, the firm believes that the average household broadcast receiver would experience no interference.

Measuring the wavelengths with the wave meter gave the following fundamental wavelengths: for the tube circuit about 2,250 kilocycles, for the gap circuit about 7,025 kilocycles.

The Council's clinical investigation revealed that the apparatus can be used to cover the field of electrosurgery. The unit's



Schematic diagram of circuit.

special feature which combines tube-current cutting with spark-gap desiccation for hemorrhage control is a useful innovation. The mechanical construction of the equipment seemed satisfactory.

The Council voted to accept the Birtcher Electro-Surgical Unit Model 799, for inclusion on its list of accepted devices.

### FINDLEY FOLDING PESSARY ACCEPTABLE

Manufacturer: American Medical Specialties Company, Inc., 12 East Twelfth Street, New York.

The Findley Folding Pessary is an appliance made in the shape of the conventional vaginal pessary but different in that a section at each end is replaced by a solid soft rubber insert. This rubber insert acts as a hinged joint so that the lateral rigid arms of the hard rubber may be swung together.

The firm states: "The Findley Folding Pessary enables the Gynecologist to place the correct sized pessary through the smallest introitus which because of the non-conformability of the regular type pessary is not possible. . . . It may be used on postpartum cases as early as ten days after delivery, or in most vaginal cases without putting strain on the pelvic floor. . . . The antero-posterior pressure of the walls holds the pessary in place and prevents it from sliding out inopportunist."



Findley Folding Pessary.

Evidence was submitted by the firm to substantiate the usefulness of the device.

The Council's clinical investigation of the device revealed that the pessary can be introduced more easily through the vaginal introitus than a solid rubber pessary. It holds the uterus in position as satisfactorily as a device made of solid rubber. The main advantages are the greater ease and the lessened discomfort associated with its introduction. A disadvantage lies in the fact that the soft rubber hinges are less easy to keep clean and free of bacterial invasion than is a device made of hard rubber. It is of value in cases in which the pain and difficulty of insertion of the usual hard rubber pessary would preclude its use.

The Council voted to accept the Findley Folding Pessary for inclusion on its list of accepted devices.

## Council on Foods and Nutrition

### ACCEPTED FOODS

THE FOLLOWING ADDITIONAL FOODS HAVE BEEN ACCEPTED AS CONFORMING TO THE RULES OF THE COUNCIL ON FOODS AND NUTRITION OF THE AMERICAN MEDICAL ASSOCIATION FOR ADMISSION TO ACCEPTED FOODS.

FRANKLIN C. BING, Secretary.

### PREPARATIONS USED IN THE FEEDING OF INFANTS (See Accepted Foods, p. 156).

The Larsen Company, Green Bay, Wis. Product Distributed by Jack Sprat Foods, Inc., Marshalltown, Iowa.

JACK SPRAT BRAND STRAINED VEGETABLES WITH BEEF AND LIVER CONCENTRATES, a canned, strained mixture of carrots, potatoes, tomatoes, peas, celery, spinach, soya bean, beef extract and liver extract.

Analysis (submitted by manufacturer).—Moisture 85.3%, total solids 14.7%, ash 1.3%, fat (ether extract) 0.1%, proteins (N  $\times$  6.25) 3.2%, crude fiber 0.7%, carbohydrates other than crude fiber (by difference) 9.4%, calcium 0.031%, phosphorus 0.072%, iron 0.0014%.

Calories.—0.51 per gram; 15 per ounce.

Product distributed by Red & White Corporation, Chicago.

RED & WHITE BRAND STRAINED VEGETABLES WITH BEEF AND LIVER CONCENTRATES, a canned, strained mixture of carrots, potatoes, tomatoes, peas, celery, spinach, soya bean, beef extract and liver extract.

Analysis (submitted by manufacturer).—Moisture 85.3%, total solids 14.7%, ash 1.3%, fat (ether extract) 0.1%, proteins (N  $\times$  6.25) 3.2%, crude fiber 0.7%, carbohydrates other than crude fiber (by difference) 9.4%, calcium 0.031%, phosphorus 0.072%, iron 0.0014%.

Calories.—0.51 per gram; 15 per ounce.

Product distributed by Schwabacher Bro's. & Co., Inc., Seattle.

HAPPY HOME BRAND STRAINED VEGETABLES WITH BEEF AND LIVER CONCENTRATES, a canned, strained mixture of carrots, potatoes, tomatoes, peas, celery, spinach, soya bean, beef extract and liver extract.

Analysis (submitted by manufacturer).—Moisture 85.3%, total solids 14.7%, ash 1.3%, fat (ether extract) 0.1%, proteins (N  $\times$  6.25) 3.2%, crude fiber 0.7%, carbohydrates other than crude fiber (by difference) 9.4%, calcium 0.031%, phosphorus 0.072%, iron 0.0014%.

Calories.—0.51 per gram; 15 per ounce.

### UNCLASSIFIED AND MISCELLANEOUS FOODS—BAKING POWDER, CREAM OF TARTAR AND BAKING SODA (See Accepted Foods, 1939, p. 376).

L. H. Kassel & Co., Fort Worth, Texas.

DIAL BRAND BAKING SODA, conforming to U. S. P. standards for pure sodium bicarbonate.

# THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

535 NORTH DEARBORN STREET - - - CHICAGO, ILL.

Cable Address - - - - "Medic, Chicago"

Subscription price - - - - Eight dollars per annum in advance

*Please send in promptly notice of change of address, giving both old and new; always state whether the change is temporary or permanent. Such notice should mention all journals received from this office. Important information regarding contributions will be found on second advertising page following reading matter.*

SATURDAY, JANUARY 11, 1941

## ANNUAL DUES NOW PAYABLE

For the convenience of those who have not paid their Fellowship dues for the coming year, a colored slip is enclosed in this issue of THE JOURNAL. This insert takes the place of a personal bill. When folded and sealed, it forms a return envelop already addressed and requiring no postage. If your dues are not paid for the coming year, please use the colored form and remit now so that no further reminder need be sent. All the periodicals of the Association with their respective subscription prices are listed on this slip, which affords an opportunity not only to pay the subscription to THE JOURNAL but also to enter subscriptions for one or more of the special journals and for *Hygeia*, the Health Magazine.

## THE OLD CONGRESS PASSES, THE NEW BEGINS

The Seventy-Sixth Congress came to a close automatically January 3 at noon without completing action on a wide variety of proposals of interest to the medical profession. Included in these proposals were reflections of many peculiar conceptions of difficulties with the American system for the distribution of medical care and even stranger notions as to how defects might be corrected. Undoubtedly most of the proposals were prompted by sincere, humanitarian motives.

The expiration of the Congress has wiped the legislative slate clean of the Wagner national health bill and the Wagner-George hospital construction bill, both of which died in the House Committee on Interstate and Foreign Commerce. A similar fate, but in various committees, overtook such measures as the Mead hospital construction bill, the Tolan bill to subject injured federal employees entitled to the benefits of the United States Employees' Compensation Act to the chiropractic thrust, the McCormack bill to compel the Army and Navy Medical Corps to accept graduates of substandard schools, cult or otherwise, and the so-called Capper-Epstein compulsory health insurance

bill. Federal appropriations which failed to be approved were proposed in bills to devolve on the United States Department of Labor jurisdiction over industrial conditions hazardous to the health of employees, to enable the states better to control various types of diseases, such as pneumonia, influenza, the common cold, tuberculosis and epilepsy, and to foster researches, investigations, experiments and studies relating to the cause, diagnosis and treatment of dental disease. The appointment of female dietitians and female physical therapy aids in the Medical Department of the Army failed to receive Congressional approval, as did also a proposal to establish a Chiropody Corps in the Army and Navy.

While a bill proposing to establish a federal department of health, a consummation long advocated by the American Medical Association, was not advanced along its legislative course, the President did, under authority of the Reorganization Act, initiate what possibly may be the beginning of a movement to associate in the Federal Security Agency functions exercised by various branches of the government having to do with matters pertaining to health. To that agency, for example, have been transferred the United States Public Health Service from the Treasury Department, the Food and Drug Administration from the Department of Agriculture, and the administration of St. Elizabeth's Hospital, Freedmen's Hospital and the Columbia Institution for the Deaf from the Department of Interior.

The Ramspeck civil service extension bill was approved by the President November 26 but before enactment the Hatch amendment was stricken from it. This proposed, in effect, to pave the way for the appointment of graduates of substandard medical schools and of cult schools in the United States Public Health Service, the Veterans' Administration, the Indian Service and to positions in other civil branches of the government. Action was not taken on the Murray-McCormack proposal to exempt medical and dental students, interns and resident physicians of recognized hospitals from the Selective Training and Service Act and to provide for the appointment of graduates of recognized medical and dental schools as commissioned officers in the Medical Department Reserve, Officers' Reserve Corps. The belief seems to prevail that through administrative procedures the desirable objectives sought by this bill can be obtained without the enactment of any additional legislation.

The establishment of a National Physical Fitness Institute, as contemplated in a bill introduced by Senator Walsh of Massachusetts, did not receive consideration by the Senate Committee on Education and Labor, to which the bill was referred, and the House Committee on Education failed to give attention to a bill sponsored by the American Association for Health, Physical Education, and Recreation and introduced by Representative Schwert of New York. This measure

proposed to enact a National Preparedness Act of 1940 for Health Education, Physical Education, and Recreation in Schools and School Camps.

Again the Congress has ended without providing adequate facilities for housing the Army Medical Library and Museum. The sum of \$130,000 was authorized for the preparation of plans for a new building. Once more *THE JOURNAL* records the fervent hope that this urgent project will not be longer delayed. The Library and Museum contains an invaluable, unique and irreplaceable collection of scientific material at present housed in a veritable fire trap. Any delay in this matter is too long.

The first session of the Seventy-Seventh Congress convened immediately on the expiration of the third session of the Seventy-Sixth Congress. Many proposals of interest to physicians will undoubtedly be presented to the new Congress for consideration. Some of the measures here mentioned, it has already been announced, will be introduced in new form. *THE JOURNAL* will continue, as in the past, to keep physicians advised promptly concerning the more important of such proposals.

#### A NEW COMPLEX INFLUENZA VACCINE

The new vaccine against influenza recently described by Horsfall and Lennette<sup>1</sup> of the Rockefeller Foundation challenges conventional immunologic theory. The vaccine seems to have been a purely accidental discovery. About a year ago, numerous normal ferrets were inoculated intranasally in the Rockefeller Foundation laboratory with the 1939 strain of human influenza virus. During the course of the resulting influenza, four of these animals developed a concurrent infection with ferret distemper. In order to prevent the spread of this epizootic to the stock animals, a formalized vaccine was prepared from the lungs and spleens of these ferrets and injected subcutaneously into each of the 157 normal animals of the ferret colony. Similar vaccines had been found effective in preventing the spread of ferret distemper on previous occasions. Two days after inoculation with this presumptive distemper vaccine, groups of the vaccinated ferrets were inoculated intranasally with massive doses of three antigenically distinct strains of human influenza virus. To the great surprise of the New York investigators, none of these animals developed experimental influenza. Injection of the presumptive distemper vaccine had apparently resulted in immunity effective against at least three antigenically different strains of influenza virus. This is a broader and more effective immunity than results from actual infection with the influenza virus.<sup>2</sup>

After numerous failures it was found possible to reproduce this multivalent vaccine by inoculating ferrets simultaneously with mixtures of human influenza virus and canine distemper virus. The formalized vaccines thus produced not only protected ferrets against canine distemper but afforded almost absolute protection against massive intranasal doses of all strains of human influenza virus thus far tested. These vaccines have been tested on human volunteers. In all instances they produced a definite increase in multivalent virucidal antibodies, apparently active against the available strains of human influenza virus.

In their latest studies of the new complex vaccine, Horsfall and Lennette<sup>3</sup> have ruled out the possibility that the observed effects are due to antigenic similarities between the influenza and distemper virus. Their evidence has led them to the conclusion that under the influence of concurrent distemper infection the human influenza virus undergoes antigenic alterations which render it less virulent, less highly specific and more broadly antigenic than the original virus. The exact nature of this hypothetical biochemical mutation is now under investigation.

Routine vaccinations of ferrets with viable human influenza virus does not result in the development of a complete immunity even against homologous strains, although a partial homologous immunity may result.<sup>4</sup> The demonstration that the new vaccine stimulates the development of a multivalent immunity, therefore, is one of the most promising practical leads in research of recent decades. Whether or not similar vaccines will be effective with other virus diseases has not yet been determined.

#### VITAMIN K AND CHOLEMIC BLEEDING

The fascinating story of the discovery of vitamin K has been the subject of editorial comment in *THE JOURNAL*<sup>1</sup> and of two comprehensive preliminary reports.<sup>2</sup> More recent contributions deal with the therapeutic possibilities of the vitamin particularly in the hemorrhagic diathesis associated with obstructive jaundice and prothrombin deficiency.

Dam of Copenhagen observed that chicks reared on an artificial fat free diet developed cutaneous and intramuscular hemorrhages and erosions of the gizzard. He reported in 1935 that the deficiency factor responsible for the hemorrhagic disease in these chicks was a fat soluble substance which he designated as "koagulations" vitamin, or vitamin K. The vitamin therefore

3. Horsfall, F. L., Jr., and Lennette, E. H.: *J. Exper. Med.* **72**: 247 (Sept.) 1940.

4. Smith, Wilson; Andrews, C. H., and Laidlaw, P. P.: *Brit. J. Exper. Path.* **16**: 291 (June) 1935. Francis, Thomas: *J. Exper. Med.* **69**: 283 (Feb.) 1939.

1. Vitamin K, editorial, *J. A. M. A.* **113**: 417 (July 29) 1939.

2. Snell, A. M.: *Vitamin K: Its Properties, Distribution and Clinical Importance*, *J. A. M. A.* **112**: 1457 (April 15) 1939. Snell, A. M., and Butt, H. R.: *Supplementary Report on Vitamin K*, *ibid.* **113**: 2056 (Dec. 2) 1939.

1. Horsfall, F. L., Jr., and Lennette, E. H.: *Science* **91**: 492 (May 24) 1940.

2. Horsfall, F. L., Jr., and Lennette, E. H.: *J. Bact.* **39**: 56 (Jan.) 1940.

may be defined as a specific fat soluble substance the absence of which in the diet of chicks causes the blood to become slow in clotting.

Vitamin K is widely distributed in nature. Concentrates of the vitamin have been prepared from alfalfa and from putrefied fish meal. The human being obtains vitamin K from the diet and from bacterial activity in the intestine. A deficiency develops when absorption of this substance from the intestine is interrupted. Faulty absorption occurs when bile is excluded from the intestine. Without bile or bile salts the vitamin cannot be absorbed.

The next problem was to isolate the vitamin in a pure form and to synthesize it. Dam, Karrer and their co-workers<sup>3</sup> isolated the vitamin in a pure or nearly pure form. Almquist and Klose<sup>4</sup> in this country announced the discovery of the antihemorrhagic activity of pure synthetic phthiocol. They expressed the opinion that phthiocol is probably the simplest member of a homologous series of antihemorrhagic substances. Phthiocol was first isolated by Anderson and Newman from the pigment of *Microbacterium tuberculosis*. McKee, Binkley, MacCorquodale, Thayer and Doisy<sup>5</sup> demonstrated that the structure of vitamin K is represented by the formula 2-methyl-3-phytyl-1, 4-naphthoquinone. The most potent of the synthetic preparations so far assayed is 2-methyl 1, 4-naphthoquinone.

In the course of continued research, a hemorrhagic diathesis in the presence of jaundice was found to be the result not of any alteration in the amounts present of calcium, bilirubin, platelets, fibrinogen or thromboplastin but of lack of vitamin K with a deficiency in levels of prothrombin. Hawkins and Whipple have described in dogs with bile fistula a tendency to bleed which is prevented by feeding whole bile. Hawkins and Brinkhous showed that the bleeding is due to deficiency of prothrombin. Quick, Stanley, Brown and Bancroft suggested that low prothrombin values may occur in obstructive jaundice. Warner, Brinkhous and Smith<sup>6</sup> demonstrated that the bleeding tendency in patients with obstructive jaundice and biliary fistula is due to a deficiency of prothrombin and that with restoration of bile to the intestine the level of prothrombin gradually returns to normal and the bleeding ceases. Feeding of alfalfa extract rich in vitamin K, in addition to bile, caused a more rapid return of the prothrombin level to normal.

The composition of prothrombin is not known. The substance is identified by its capacity to form thrombin. Smith, Warner and Brinkhous demonstrated the inti-

mate relationship between plasma prothrombin and liver function by damaging the livers of dogs with chloroform or by partial hepatectomy in rats. In the light of recent research it appears probable that the seat of formation of prothrombin is the liver. Vitamin K is essential to the process of coagulation of blood. It is ingested in our diets and is absorbed from the intestinal epithelium in the presence of bile.

Clinical application has demonstrated the significance of vitamin K in restoration of the plasma prothrombin to a normal level and the importance of bile salts in influencing its absorption from the intestinal tract. Butt, Snell and Osterberg<sup>7</sup> reported 127 cases of jaundice of various types. In the majority, bleeding has been adequately controlled by the administration of concentrates of vitamin K and bile salts. In a later communication the same authors<sup>8</sup> report on the use of phthiocol in ten cases of hypoprothrombinemia. In each instance the elevated prothrombin time was reduced to a near normal level. Rhoades and Fliegelman<sup>9</sup> report on the effect of 2-methyl 1, 4-naphthoquinone, the most potent of the synthetic preparations so far assayed. Ten patients with demonstrated prothrombin deficiencies responded satisfactorily to doses of from 1 to 4 mg. a day orally.

In a recent communication Andrus and Lord<sup>10</sup> published a report of twenty-two cases of biliary disease and low prothrombin level in which vitamin K and bile salts were administered. They were able uniformly to bring about a cessation of bleeding. In a more recent group of thirty-eight cases these authors used the synthetic substance 2-methyl 1, 4-naphthoquinone. They state that this substance is inexpensive and that intramuscular injection of it dissolved in corn oil is so simple and effective that they believe it to be the simplest method of administration in the treatment of prothrombin deficiencies. When it is given by injection the presence of bile salts in the intestinal tract is not necessary for its absorption and its effect is evident within a few hours. All experimental and clinical observations tend to show that the integrity of the hepatic parenchyma is the controlling factor, since it is the seat of formation of prothrombin and of the synthesis of vitamin K. Thus vitamin K is ineffective in the presence of cirrhosis of the liver or a severe hepatitis. It is without value in hemophilia or in thrombocytopenic purpura, since in these cases there is no deficiency in prothrombin or vitamin K.

3. Dam, H.; Geiger, A.; Glavind, J.; Karrer, P.; Karrer, W.; Rothchild, E., and Salomon, H.: Isolierung des Vitamins K in hochgereinigter Form, *Helvet. chim. acta* **22**: 310 (March) 1939.

4. Almquist, H. J., and Klose, A. A.: The Antihemorrhagic Activity of Certain Naphthoquinones, *J. Am. Chem. Soc.* **61**: 1611 (June) 1939.

5. McKee, R. W.; Binkley, S. B.; MacCorquodale, D. W.; Thayer, S. A., and Doisy, E. A.: The Isolation of Vitamin K<sub>1</sub> and K<sub>2</sub>, *J. Am. Chem. Soc.* **61**: 1295 (May) 1939.

6. Warner, E. D.; Brinkhous, K. M., and Smith, H. P.: Bleeding Tendency of Obstructive Jaundice: Prothrombin Deficiency and Dietary Factor, *Proc. Soc. Exper. Biol. & Med.* **37**: 228 (Jan.) 1938.

7. Butt, H. R.; Snell, A. M., and Osterberg, A. E.: The Preoperative and Postoperative Administration of Vitamin K, *J. A. M. A.* **112**: 383 (July 29) 1939.

8. Butt, H. R., and Snell, A. M.: Phthiocol: Its Therapeutic Effect in the Treatment of Hypoprothrombinemia Associated with Jaundice: A Preliminary Report, *Proc. Staff Meet., Mayo Clin.* **14**: 497 (Aug. 9) 1939.

9. Rhoades, J. E., and Fliegelman, M. T.: The Use of 2-Methyl-1, 4-Naphthoquinone (A Synthetic Vitamin K Substitute), *J. A. M. A.* **114**: 400 (Feb. 3) 1940.

10. Andrus, W. D., and Lord, J. W., Jr.: Clinical Investigations of Some Factors Causing Prothrombin Deficiencies, *Arch. Surg.* **41**: 596 (Sept.) 1940.



## Current Comment

### ACETYSALICYLIC ACID DEATHS

Recently an editorial on the toxicity of acetylsalicylic acid appeared in these columns.<sup>1</sup> Since that time several communications have been received commending *THE JOURNAL* for publishing the editorial. One correspondent asserted that he knew of two instances in which only prompt medical attendance saved the lives of two colleagues who had ingested the drug. He also was aware of a prominent dermatologist who developed such intense pharyngeal and laryngeal edema after taking aspirin that a tracheotomy was about to be performed when the edema began to subside. Again, an allergist had informed him of at least five deaths attributed to acetylsalicylic acid. Another correspondent wrote of a patient who had taken 250 grains (16 Gm.) of acetylsalicylic acid daily for a period of ten days. The patient recovered following treatment directed chiefly toward elimination of the drug, control of acidosis and relief of other symptoms. There must be many more cases of drug intoxication or poisoning than are reported in medical literature. Often only by accident are these brought to the attention of the medical profession. Obviously case reports of such conditions affecting human beings are an invaluable contribution to our practical knowledge of toxicology. On the other hand, the toxicity of aspirin, in relation to the amounts used annually, still must be rated as low.

### DENSITY OF WORLD POPULATIONS

Some regions of the earth's surface are much more heavily populated than others. For example, the continents of North and South America are far less crowded in proportion to the ability of the land to support their inhabitants than is the continent of Europe. Pearl<sup>1</sup> points out that this contrast is not necessarily permanent; at least some of the nations of the Western Hemisphere are growing in population at rates which if continued will sooner or later materially alter the favorable ratios which they now possess. There are six attributes of populations, he says, that are generally regarded as of primary importance: (1) the density of aggregation per unit of land area, (2) the net over-all percentage rate of growth per unit of time, (3) the natural rate of increase by excess of births over deaths, (4) the age composition, (5) the "racial" composition and (6) the so-called quality, as variously appraised through what the psychologists test under the designation "intelligence" or by other criteria or combinations. The four principal attributes which can be objectively measured lead to the conclusion that the populations of the Western Hemisphere are at present in a relatively much more favorable position biologically and demographically than are those of the Eastern Hemisphere. The fundamental problem facing the populations in the Western World is what they are going to make of the future

that lies before them. It needs no great prophet, Pearl emphasizes, to foresee that after the present conflict is ended enormous pressure will be exerted on the peoples of the Western Hemisphere to take immigrants from the Old World and share with them the acres that are still relatively so sparsely populated. It is equally certain, he believes, that should the gates be thrown wide open it would be a comparatively short time in terms of human history until the average population density of our hemisphere would be as great as that of the Old World today. Although this forecast, like all prophecies, is an uncertain quantity, one cannot but agree with Pearl "that the immediate establishment of national population policies soundly grounded scientifically is an imperative obligation upon the peoples of the Americas." Also it is probably safe to conclude that the relatively favorable position reflected in a population density of 16.5 persons to the square mile in the Western, as compared with 57 in the Eastern, Hemisphere plays a large part in the relative freedom from economic strife manifest between nations in the Americas.

### THE STATISTICS ON SYPHILIS

Recent announcements and bulletins issued by various agencies of the federal government have quoted varying rates for the incidence of syphilis. Thus, one pamphlet states that there are 224 new cases annually for each hundred thousand of the population. A poster, however, carries the statement "A million new victims each year." In an endeavor to determine the method by which such figures were reached, a letter was addressed to the Division of Venereal Diseases of the United States Public Health Service, and the following information is supplied: The figure 224 per hundred thousand represents an annual attack rate, based on census material assembled in 1936-1937, indicating the known number of cases of syphilis of less than one year's duration in which treatment was sought from an authorized source of treatment. The second statement, namely "A million new victims each year," is a rate based on information assembled from 1927 to 1930 through surveys of authorized sources of treatment. These reports indicated that 518,000 persons with early syphilis sought medical care and an additional half million persons sought similar care for the first time, although their infections had passed the early stages of the disease. The explanation is, then, that in the lower rates only those seeking medical care for early syphilis are reported, whereas in the higher figure an additional half million persons who failed to seek treatment during the first year of the disease but did so later are included in the statement "A million new victims each year." In other words, this estimate of a million assumes that each year a half million persons contract the disease who do not seek medical care during the early stages but do so later. Would it not be wholly an assumption that there are each year a half million new cases and a half million old cases in which it is decided for the first time to seek treatment? The Division of Venereal Diseases points out that further studies are under way and it is hoped to supply more satisfactory statements on the incidence of syphilis in our times.

1. Acetylsalicylic Acid Deaths, *Current Comment*, J. A. M. A. **115**: 1199 (Oct. 5) 1940.

1. Pearl, Raymond: A Comparative Examination of Certain Aspects of the Populations of the New World, *Human Biology* **12**: 359 (Sept.) 1940.

# MEDICAL PREPAREDNESS

*In this section of The Journal each week will appear official notices by the Committee on Medical Preparedness of the American Medical Association, announcements by the Surgeon Generals of the Army, Navy and Public Health Service, and other governmental agencies dealing with medical preparedness, and such other information and announcements as will be useful to the medical profession.*

## COMMISSIONS IN MEDICAL CORPS OF U. S. NAVY

Applications for commissions as medical officers in the U. S. Navy are now being received in the Bureau of Medicine and Surgery, Navy Department, Washington, D. C. Examinations for entrance into the Medical Corps of the regular Navy will be held on May 12 to 15, inclusive, 1941, at all of the larger naval hospitals, including those at Chelsea (Boston), Mass., Brooklyn, Philadelphia, Portsmouth (Norfolk), Va., Great Lakes, Ill., Charleston, S. C., Pensacola, Fla., San Diego, Calif., Mare Island, Calif., Puget Sound (Bremerton), Wash., and at the Naval Medical Center, Washington, D. C. Successful candidates from this examination will receive their appointments approximately two months from the date of the examination.

Applicants are required to be citizens of the United States between 21 and 32 years of age at the time of appointment, graduates of a class A medical school, and to have completed at least one year of intern training in a hospital accredited for intern training by the Council on Medical Education and Hospitals of the American Medical Association. They are required to be physically qualified and to demonstrate their professional qualifications by written, oral and practical examinations embracing the subjects of general medicine, general

surgery, obstetrics and gynecology, and preventive medicine and jurisprudence. The physical and professional examinations usually require from three to four days for completion.

Successful candidates are commissioned as assistant surgeons with the rank of lieutenant (junior grade) in the Medical Corps of the Navy. An officer of this rank receives compensation of \$2,699 a year if he has no dependents and \$3,158 a year if he has dependents.

A "Circular for the Information of Persons Desiring to Enter the Medical Corps of the United States Navy," including data pertaining to physical requirements, promotion and retirement, may be obtained by addressing a request to the Surgeon General of the Navy, Navy Department, Washington, D. C.

## PHYSICIANS WANTED FOR CCC CAMPS

Full time positions are available for physicians in the Sixth Corps Area (Illinois, Michigan and Wisconsin) for medical work in the Civilian Conservation Corps. Only graduates of class A medical schools are acceptable, and they must be licensed to practice in at least one state and must be physically qualified. Further information may be obtained from the surgeon, Sixth Corps Area, New P. O. Building, Chicago.

## ARMY RESERVE OFFICERS ORDERED TO ACTIVE DUTY WAR DEPARTMENT

The following additional medical reserve corps officers had been ordered to extended active duty with the regular army by direction of the War Department, Washington, D. C., up to Dec. 27, 1940:

AUSHERMAN, Howard Milton, 1st Lieut., Chattanooga, Tenn.  
BIERNOFF, Joseph, 1st Lieut., San Francisco.  
CHESTER, Benjamin Joseph, 1st Lieut., Brooklyn.  
CONEN, Warren Joseph, 1st Lieut., Milwaukee.  
FITZSIMMONS, William Richard, 1st Lieut., Zelenople, Pa.  
FREE, Richard Mathew, Captain, Coatesville, Pa.  
KANE, David Saul, 1st Lieut., Chicago.  
KENDRICK, James E., Jr., 1st Lieut., Greenville, Ala.  
KOLODNY, Sydney Maurice, 1st Lieut., Chicago.

KREINDLER, Louis, 1st Lieut., Cincinnati.  
KYSOR, Benjamin Bennett, Jr., 1st Lieut., Madrid, N. M.  
LORD, Herman McNeill, 1st Lieut., Chelsea, Mich.  
MARGOLIS, Meyer Nathan, 1st Lieut., Cincinnati.  
MILLER, Earl Edward, 1st Lieut., Washington, D. C.  
MYERS, Martin Alexander, 1st Lieut., Philadelphia.  
O'CONNELL, William Michael, 1st Lieut., Peoria, Ill.  
OLSEN, Orland Stenberg, 1st Lieut., Sioux Falls, S. D.  
ROTHMAN, Leonard Edward, 1st Lieut., Milwaukee.  
SIRLIN, Edward Martin, 1st Lieut., Moultrie, S. C.  
SOWERS, John William, 1st Lieut., Fayetteville, Pa.  
SUTTON, Robert Stamper, 1st Lieut., San Antonio, Texas.  
VICTOR, Samuel Allan, 1st Lieut., Omaha.  
WISE, Albert Walter, 1st Lieut., Peoria, Ill.  
WOLFE, Russell Sheldon, 1st Lieut., Houston, Texas.

## FIRST CORPS AREA

The following additional medical reserve corps officers had been ordered to extended active duty with the regular army by the Commanding General, First Corps Area, up to Dec. 20, 1940. The First Corps Area comprises the states of Maine, Vermont, New

Hampshire, Rhode Island, Massachusetts and Connecticut.

GILLESPIE, Harry, Lieut., Hartford, Conn.  
NASH, William C., 1st Lieut., Beverly, Mass.  
SKOOG, Allan P., 1st Lieut., Rutland, Mass.

## THIRD CORPS AREA

The following additional medical reserve corps officers had been ordered to extended active duty by the Commanding General, Third Corps Area, up to Dec. 27, 1940. The Third Corps Area comprises the states of Pennsylvania, Virginia, District of Columbia and Maryland.

ADAMS, Harry Albert, 1st Lieut., Hanover, Pa., Fort George G. Meade, Md.  
BAILL, Myron Henry, 1st Lieut., Scranton, Pa.

BELL, Robert Franklin, 1st Lieut., Petersburg, Va., Camp Lee, Va.  
BOAS, Harry, 1st Lieut., Pittsburgh.  
CONFAIR, William Freas, Captain, Benton, Pa.  
CORLEY, Karl Coates, 1st Lieut., Chevy Chase, Md.  
CRIST, George Bruce, Major, Frederick, Md., Camp Lee, Va.  
DAPARMA, Frank Louis, 1st Lieut., Pittsburgh.  
DICK, Arthur, 1st Lieut., Washington, D. C.  
DRISCOLL, Thomas Latane, Major, Columbia, Va.  
HAYES, Merrill B., 1st Lieut., Upland, Pa.  
JONES, Eugene M., 1st Lieut., North Braddock, Pa.  
KANE, James Aloysius, 1st Lieut., Philadelphia, Camp Lee, Va.

KATZ, Samuel Herschel, 1st Lieut., Philadelphia.  
KAUFMAN, Irwin Leonard, Captain, Pittsburgh.  
MacNEAL, Herbert Pratt, 1st Lieut., Philadelphia.  
MANCUSO, Joseph Arthur, 1st Lieut., Meadville, Pa.  
MONTGOMERY, Edward S., 1st Lieut., Tarentum, Pa.  
REED, Paul Allen, 1st Lieut., Washington, D. C.  
REESE, Evan Charles, 1st Lieut., East Stroudsburg, Pa.  
ROSENBERG, Seymour Joseph, Captain, Baltimore.

### SIXTH CORPS AREA

The following additional medical reserve corps officers had been ordered to extended active duty by the Commanding General, Sixth Corps Area, up to Dec. 27, 1940. The Sixth Corps Area comprises the states of Wisconsin, Illinois and Michigan.

ANKNER, Frank J., 1st Lieut., Thief River Falls, Minn.  
BALDING, Bruce Ned, 1st Lieut., Elgin, Ill.  
BARAK, Herbert G., 1st Lieut., Dixon, Ill.  
EPSTEIN, David, 1st Lieut., Chicago.  
HUTH, Melvin F., 1st Lieut., Baraboo, Wis.  
KAISER, Jerome, 1st Lieut., Chicago.  
KAUFMAN, Lawrence W., 1st Lieut., Milwaukee.  
KOCOVSKY, Clarence J., 1st Lieut., Wauwatosa, Wis.

### SEVENTH CORPS AREA

The following additional medical reserve corps officers had been ordered to extended active duty by the Commanding General, Seventh Corps Area, up to Dec. 27, 1940.

The Seventh Corps Area comprises the states of North Dakota, South Dakota, Minnesota, Nebraska, Iowa, Kansas, Missouri, Arkansas and Wyoming.

SANDHAUS, Julius Louis, 1st Lieut., Lancaster, Pa.  
SCHLECHTER, Charles F., 1st Lieut., Philadelphia.  
SCHUCHET, George, 1st Lieut., Cockeysville, Md., Fort Belvoir, Va.  
SHARP, Edward George, 1st Lieut., Philadelphia.  
SPEAR, Paul William, 1st Lieut., Baltimore.  
UNDERWOOD, Harry Burnham, 1st Lieut., Bangor, Pa.  
WITKIN, Leon Abba, 1st Lieut., Philadelphia.  
ZEHFUSS, Paul Edward, Captain, Pittsburgh.

KLEIN, Max E., 1st Lieut., Milwaukee.  
LATIMER, Earl O., 1st Lieut., Chicago.  
LEASUM, Charles R., 1st Lieut., Sturgeon Bay, Wis.  
LEE, Harry, 1st Lieut., Milwaukee.  
MOLL, Clarence D., Major, Detroit.  
RAINE, Forrester, Captain, Milwaukee.  
ROSENTHAL, Irving H., 1st Lieut., Chicago.  
ROSENTHAL, Martin J., Captain, LaSalle, Ill.  
RUTHLEDGE, James H., Major, Nebo, Ill.  
SCHAEFFER, Bernard J., 1st Lieut., Chicago.  
SCHIELE, William C., Major, Galena, Ill.  
SMITH, Herschell S., 1st Lieut., East St. Louis, Ill.  
STEIN, Phillip J., 1st Lieut., Chicago.  
SUMMERS, Thomas F., 1st Lieut., Olney, Ill.

AUTRY, Daniel Hill, 1st Lieut., Rochester, Minn., Camp Joseph T. Robinson, Ark.  
CULBERTSON, Robert A., Major, St. Ansgar, Iowa, Camp Joseph T. Robinson, Ark.  
MORTON, William Adler, 1st Lieut., Vandalia, Mo., Fort Snelling, Minn.  
PROCHAZKA, Otto Frank L., 1st Lieut., Wichita, Kan., Camp Joseph T. Robinson, Ark.  
USHER, Francis Cowgill, Captain, Rochester Minn., Camp Joseph T. Robinson, Ark.

## NAVAL RESERVE OFFICERS ORDERED TO ACTIVE DUTY

The following additional U. S. Navy medical reserve officers had been ordered to active duty at the stations indicated up to Dec. 21, 1940:

CLARK, Frank B., Lieut., M. C.-V. (S.), Austell, Ga., Headquarters, Eighth Naval District.  
CLASEN, Arthur C., Lieut. Comdr., M. C.-V. (G.), Kansas City, Kan., Second Marine Brigade, Fleet Marine Force, Marine Corps Base, San Diego, Calif.  
COLEY, Joe Henry, Lieut. (j. g.), M. C.-V. (G.), Oklahoma City, Second Marine Brigade, Fleet Marine Force, Marine Corps Base, San Diego, Calif.  
COWAN, John Stephen, Lieut. (j. g.), M. C.-V. (G.), Detroit, Second Marine Brigade, Fleet Marine Force, Marine Corps Base, San Diego, Calif.  
COYER, Howard Arthur, Lieut. (j. g.), M. C.-V. (G.), New Cumberland, Pa., First Marine Brigade, Fleet Marine Force, Quantico, Va.  
EISENBERG, Harry, Lieut. (j. g.), M. C.-V. (G.), New York, First Marine Brigade, Fleet Marine Force, Quantico, Va.  
ESTES, Sol B., Lieut., M. C.-V. (G.), Abilene, Texas, Second Marine Brigade, Fleet Marine Force, Marine Corps Base, San Diego, Calif.  
FREEDMAN, Saul, Lieut., M. C.-V. (S.), New York, Navy Yard Dispensary, Navy Yard, New York.  
GIDDING, Samuel S., Lieut. (j. g.), M. C.-V. (G.), Wildwood, N. J., First Marine Brigade, Fleet Marine Force, Quantico, Va.  
GLENN, Herbert Ross, Lieut. (j. g.), M. C.-V. (G.), State College, Pa., First Marine Brigade, Fleet Marine Force, Quantico, Va.  
GLOCKER, Rudolph K., Lieut., (j. g.) M. C.-V. (G.), Royersford, Pa., First Marine Brigade, Fleet Marine Force, Quantico, Va.  
GRANET, Emil, Lieut., M. C.-V. (S.), New York, Naval Hospital, Brooklyn.  
HAIGHT, Harry Hurlless, Lieut. M. C.-V. (G.), Crystal Falls, Mich., Second Marine Brigade, Fleet Marine Force, Marine Corps Base, San Diego, Calif.  
HATCHETTE, Charles V., Lieut. Comdr., M. C.-V. (G.), Lake Charles, La., Second Marine Brigade, Fleet Marine Force, Marine Corps Base, San Diego, Calif.  
ISARD, Harold Joseph, Lieut. (j. g.), M. C.-V. (G.), Philadelphia, First Marine Brigade, Fleet Marine Force, Quantico, Va.  
JENSEN, Russell M., Lieut. (j. g.), M. C.-V. (G.), Monmouth, Ill., Second Marine Brigade, Fleet Marine Force, Marine Corps Base, San Diego, Calif.  
KIENE, Richard H., Lieut. (j. g.), M. C.-V. (G.), Kansas City, Mo., Second Marine Brigade, Fleet Marine Force, Marine Corps Base, San Diego, Calif.  
KOEHLER, Joseph S., Lieut. Comdr., M. C.-V. (G.), Dayton, Ohio, Naval Hospital, Philadelphia.  
KURTZ, Gerald I., Lieut. (j. g.), M. C.-V. (G.), Paterson, N. J., Naval Hospital, Philadelphia.  
LAUTERBACH, Chester H., Lieut. (j. g.), M. C.-O., Rochester, N. Y., U. S. S. *Caster*.  
LAVICTOIRE, Isaac N., Lieut., M. C.-V. (G.), Ionia, Mich., Second Marine Brigade, Fleet Marine Force, Marine Corps Base, San Diego, Calif.

LUCKEY, Robert C., Lieut., M. C.-V. (G.), Wolf Lake, Ind., Second Marine Brigade, Fleet Marine Force, Marine Corps Base, San Diego, Calif.  
MARGRAVES, Ross D., Lieut. (j. g.), M. C.-V. (S.), Houston, Texas, Naval Air Station, Corpus Christi, Texas.  
McGRALL, Matthew A., Lieut., M. C.-V. (G.), Bradford, Pa., First Marine Brigade, Fleet Marine Force, Quantico, Va.  
McLAUGHLIN, Robert R. M., Lieut., M. C.-V. (S.), Great Neck, N. Y., Naval Hospital, Brooklyn.  
OLMSTED, George S., Lieut. (j. g.), M. C.-V. (G.), Detroit, Second Marine Brigade, Fleet Marine Force, Marine Corps Base, San Diego, Calif.  
PHILLIPS, John Reed, Lieut. Comdr., M. C.-V. (G.), Michigan City, Ind., Second Marine Brigade, Fleet Marine Force, Marine Corps Base, San Diego, Calif.  
RANDALL, Samuel Bunker, Lieut. Comdr., M. C.-V. (G.), Santa Cruz, Calif., Second Marine Brigade, Fleet Marine Force, Marine Corps Base, San Diego, Calif.  
ROBINSON, Charles G., Jr., Lieut. (j. g.), M. C.-V. (G.), Memphis, Tenn., Second Marine Brigade, Fleet Marine Force, Marine Corps Base, San Diego, Calif.  
RYAN, Harry Edward, Lieut. (j. g.), M. C.-V. (G.), Centralia, Ill., Second Marine Brigade, Fleet Marine Force, Marine Corps Base, San Diego, Calif.  
SCHLOSSBACH, Theodore, Lieut., (j. g.), M. C.-V. (G.), Ocean Grove, N. J., First Marine Brigade, Fleet Marine Force, Quantico, Va.  
SCHMIDT, Albert F., Lieut. (j. g.), M. C.-V. (G.), Manassas, N. J., First Marine Brigade, Fleet Marine Force, Quantico, Va.  
SCHNEIERSON, Sol S., Lieut., M. C.-V. (G.), New York, First Marine Brigade, Fleet Marine Force, Quantico, Va.  
SHINN, Adam Louis, Lieut., M. C.-V. (G.), Corpus Christi, Texas, Second Marine Brigade, Fleet Marine Force, Marine Corps Base, San Diego, Calif.  
SIMPSON, Frederick G., Lieut. (j. g.), M. C.-V. (G.), Wauwatosa, Wis., Second Marine Brigade, Fleet Marine Force, Marine Corps Base, San Diego, Calif.  
SKINNER, Robert W., Lieut. (j. g.), M. C.-V. (G.), Pittsburgh, First Marine Brigade, Fleet Marine Force, Quantico, Va.  
SMITH, Stanton G., Lieut. (j. g.), M. C.-V. (G.), Decatur, Ill., Second Marine Brigade, Fleet Marine Force, Marine Corps Base, San Diego, Calif.  
SYBLIRUD, Hjalmer W., Lieut. Comdr., M. C.-V. (G.), Bricelyn, Minn., Second Marine Brigade, Fleet Marine Force, Marine Corps Base, San Diego, Calif.  
THOMPSON, Ralph B., Lieut. (j. g.), M. C.-V. (G.), Lynbrook, N. Y., First Marine Brigade, Fleet Marine Force, Quantico, Va.  
TRANSUE, Seward Myers, Lieut. (j. g.), M. C.-V. (G.), Glenville, Pa., First Marine Brigade, Fleet Marine Force, Quantico, Va.  
VAIL, James B., Lieut., M. C.-V. (G.), Henning, Minn., Second Marine Brigade, Fleet Marine Force, Marine Corps Base, San Diego, Calif.  
WHITE, Raymond Ned, Lieut. (j. g.), M. C.-V. (G.), Springfield, Mo., Second Marine Brigade, Fleet Marine Force, Marine Corps Base, San Diego, Calif.

# ORGANIZATION SECTION

## OFFICIAL NOTES

### THE CLEVELAND SESSION

#### Applications for Space in the Scientific Exhibit

Applications for space in the Scientific Exhibit at the Cleveland Session, both for exhibits and for motion pictures, close on January 20. Blanks may be obtained from the section representatives or from the Director, Scientific Exhibit, American Medical Association, 535 North Dearborn Street, Chicago.

### RADIO BROADCASTS

"Doctors at Work" is the title of the sixth annual series of dramatized radio programs being presented by the American Medical Association and the National Broadcasting Company.

The series opened Wednesday, Nov. 13, 1940, and will run for thirty consecutive weeks, closing with a broadcast from the A. M. A. meeting at Cleveland on June 4. The program is scheduled for 10:30 p. m. eastern standard time (9:30 central, 8:30 mountain, 7:30 Pacific time) over the Blue network, other N. B. C. stations and Canadian stations.

The programs are broadcast on what is known in radio as a sustaining basis; that is, the time is furnished gratis by the radio network and local stations, and no revenue is derived from the programs. Therefore, local stations may or may not take the programs, at their discretion, except those stations which are owned and operated by the National Broadcasting Company.

Some radio stations may be unable to broadcast the program at the regular scheduled time and may transcribe and broadcast it at another hour or even on another day. It is advisable therefore to verify the time by reference to local newspapers or by telephoning the local Blue network stations.

The programs will dramatize what modern medicine offers the individual in the way of opportunities for better health and the more successful treatment of disease. Incidental to this main theme, the programs will explain the characteristics of the different fields of modern medicine and its specialties.

Descriptive posters for local distribution may be had gratis from the Bureau of Health Education, American Medical Association, 535 North Dearborn Street, Chicago. Program titles will be announced weekly in *THE JOURNAL* and monthly in *Hygeia*, the Health Magazine.

Tickets are available for each broadcast. Address the Bureau of Health Education, American Medical Association, 535 North Dearborn Street, Chicago. Tickets are free, but a stamped self-addressed envelop should accompany requests.

The next three programs to be broadcast, together with their dates and their titles, are as follows:

January 15. Best Foot Forward.

January 22. Blocking Pain.

January 29. Deeper Than It Looks.

## WOMAN'S AUXILIARY

### Illinois

The woman's auxiliary of the Irving Park Branch of the Chicago Medical Society, of which Mrs. Charles Stigman is president, met October 22 at the Spaulding School for Crippled Children. A tour of the institution was made. September 24 it met at the Irving Park Y. M. C. A. The Calumet branch, of which Mrs. John Soukup is president, met September 27 at the home of Mrs. J. O. Peterson. The South Chicago branch, of which Mrs. William Murray Jr. is president, met October 7 at South Shore Hospital Nurses' Home. At a benefit bridge party money was raised to be used for *Hygeia*. The North Shore branch, of which Mrs. C. I. Wynekoop is president, met October 7 at the home of Mrs. Walter Armstrong. Mrs. Barnett Smith presented some Scandinavian readings of her own composition. The Jackson Park Branch, of which Mrs. Raymond McPherron is president, met October 16 at the home of Mrs. H. P. Jenkins. Dr. Charles E. Shannon, president of the Jackson Park Branch of the Chicago Medical Society, spoke on "The Relationship Between the Branch and the Woman's Auxiliary." The North Side branch, with Mrs. A. I. Edison as president, met October 21 at the Chicago Historical Society. One hundred and five members and guests were present. Mrs. Edison gave a fine talk on the "Aims and Objectives of the Auxiliary." "Choose to Live," a moving picture sponsored by the American Society for the Control of Cancer, was shown. Mr. J. M. Pratt, executive administrator of the National Physicians' Committee, spoke on "Medical Progress." Dr. Franklin C. Bing, Secretary of the Council on Foods, spoke on "Nutrition in Relation to the National Defense." The Aux Plaines branch, with Mrs. C. W. Stuart as president, met October 25 at the home of Mrs. H. A. Soffield. Mr. F. J. Schlotfeldt of the U. S. Department of Justice, spoke on immigration and naturalization. Mrs. H. J. Dooley discussed the "Benevolence Fund" and the part the auxiliary will take.

The Peoria County auxiliary, of which Mrs. O. E. Barbour is president, met October 8 at the Creve Coeur Club. Mrs. Walter King, philanthropic chairman, announced that the auxiliary would help at the Red Cross headquarters every Tuesday afternoon. The group then joined the doctors at the Jefferson Hotel where Dr. Horton Casparis, Nashville, Tenn., gave a talk on "Mental Hygiene." A number of school teachers and principals of Peoria were invited to attend. A question and answer period followed.

The Bureau County auxiliary, with Mrs. A. R. Troupa as president, met October 10 at the Presbyterian Church. The Bureau County Medical Society and the County Lawyers and their wives were guests of the auxiliary. Dr. Paul Schroeder, state criminologist, spoke on "Prevention and Cure of Juvenile Delinquency."

The Will-Grundy County auxiliary, with Mrs. George H. Woodruff as president, met October 14 at the home of Mrs. B. S. Wilcox. Mr. Stuart Hummel, superintendent of Silver Cross Hospital, spoke on "The Hospital and Its Part in National Preparedness."

### Southern Medical Auxiliary

The Woman's Auxiliary to the Southern Medical Association met in Louisville, Ky., Nov. 13-14, 1940, during the meeting of the Southern Medical Association. The program included an address by the national auxiliary president, Mrs. V. E. Holcombe, on "Enlarging the Circulation of the Bulletin." Dr. Nathan Van Etten, President of the American Medical Association, gave an inspiring talk on "Socialized Medicine." The Kentucky organization presented a "Pageant of Pioneer Kentucky." The members of the auxiliary were guests of the Woman's Club at tea to hear Dr. Thomas Parran, chief of the United States Health Service. The new president, Mrs. M. Pinson Neal, was installed for the coming year.

## Medical News

(PHYSICIANS WILL CONFER A FAVOR BY SENDING FOR THIS DEPARTMENT ITEMS OF NEWS OF MORE OR LESS GENERAL INTEREST: SUCH AS RELATE TO SOCIETY ACTIVITIES, NEW HOSPITALS, EDUCATION AND PUBLIC HEALTH.)

### CALIFORNIA

**Personal.**—Dr. William J. Kerr, professor of medicine, University of California Medical School, San Francisco, has been elected an honorary member of the Liga Argentina contra el Reumatismo, Buenos Aires.—Dr. Henry E. Dahleen has been appointed superintendent of the Santa Clara County Hospital, San Jose, succeeding the late Dr. Fred S. Ryan. The latter had held the superintendency since the resignation of Dr. Doxey R. Wilson last summer.—Dr. Charles E. Schoff, Sacramento, has resigned as a member of the state board of health on account of ill health, it was stated.

### COLORADO

**Society News.**—Dr. Oswald S. Lowsley, New York, discussed "Prostatic Surgery" at a recent meeting of the Medical Society of the City and County of Denver, and Dr. Edgar Mayer, New York, "Pulmonary Tuberculosis in the Present Epidemiologic Phase."—The Colorado Neurological Society was addressed in Denver, December 7, among others, by Drs. Karl T. Neuburger on "Pathogenesis of Intracranial Hemorrhage," and Charles A. Rymer, "Review of Shock Therapy to Date." Dr. Franklin G. Ebaugh gave a demonstration of electric shock therapy.

### DELAWARE

**Hospital Seminar.**—The Delaware State Hospital, Farnhurst, conducted a seminar, November 24-26 and December 2-5, with the following speakers:

Dr. Bernard J. Alpers, Philadelphia, Neuropathology.  
Dr. George Hall Hyslop, New York, Clinical Neurology.  
Dr. William F. Murphy, Boston, Internal Medicine.  
Dr. Francis C. Grant, Philadelphia, Neurosurgery.  
Dr. Edward A. Strecker, Philadelphia, Psychiatry.  
Dr. Charles W. Dunn, Philadelphia, Endocrinology.

### GEORGIA

**Course for General Practitioners.**—A series of courses on venereal diseases opened at the University of Georgia School of Medicine, Augusta, November 18-30. The second was held December 2-14 and the third was to be January 6 to 18. The series is sponsored by the state department of public health in cooperation with the U. S. Public Health Service and the board of regents of the University System.

### IDAHO

**Society News.**—Dr. Nymphus F. Hicken, Salt Lake City, discussed "Thyrogenic Disturbances" before a meeting of the Southwestern Idaho District Medical Society in Boise recently.—Drs. Donald A. Palmer and Arthur E. Lien, Spokane, discussed medical and surgical complications, respectively, of pneumonia at a recent meeting of the North Idaho Medical Society in Lewiston.

### LOUISIANA

**Personal.**—Dr. De Witt T. Milam, Monroe, has been appointed superintendent of the E. A. Conway Charity Hospital. According to the state medical journal, Dr. Milam will be honorary superintendent until the hospital is opened in a few months. He is president of the Ouachita Parish Medical Society, secretary of the Louisiana State Urological Society and is regimental surgeon of the 156th Infantry.

**The Chaillé Oration.**—Dr. Frederick P. Moersch of the Mayo Clinic, Rochester, Minn., delivered the annual Chaillé Oration of the Orleans Parish Medical Society, December 3, in New Orleans. His subject was the shock treatment of major psychoses by electricity. The lecture is named for Dr. Stanford Emerson Chaillé, who died in 1911. Dr. Chaillé was once dean of the medical school now known as Tulane University of Louisiana School of Medicine, New Orleans, and in 1879 was president of an early Habana yellow fever commission.

### MARYLAND

**Society News.**—The Baltimore City Medical Society held its annual meeting December 6 with the following speakers: Drs. Max M. Strumia, Bryn Mawr, Pa., on "Plasma, Preparation, Means of Preservation, with Special Reference to the

Treatment of Shock," and John Scudder, New York, "Shock: Blood Studies as a Guide to Therapy." A symposium on diseases of the liver was presented before the society December 20 by Drs. Thomas P. Sprunt, William Halsey Barker and Moses Paulson.

**Dr. Blalock Succeeds Dr. Dean Lewis at Johns Hopkins.**—Dr. Alfred Blalock, professor of surgery, Vanderbilt University School of Medicine and visiting surgeon at Vanderbilt Hospital, Nashville, Tenn., has been appointed to a similar position at Johns Hopkins University School of Medicine and surgeon in chief to the Johns Hopkins Hospital, Baltimore. The professorship has been vacant since the retirement of Dr. Dean Lewis in the spring of 1939. A native of Culloden, Ga., Dr. Blalock graduated at Johns Hopkins in 1922. He was a member of the staff of the Johns Hopkins Hospital from 1922 to 1925 and resident surgeon at Vanderbilt Hospital from 1925 to 1927. He served as assistant professor of surgery at Vanderbilt from 1927 to 1930 and associate professor from 1930 to 1937, when he became professor. He is 41 years of age.

### MASSACHUSETTS

**Obstetric Meeting.**—The New England Obstetrical and Gynecological Society held its twelfth annual meeting in Boston, December 4. The speakers included:

Robert Kark, B. A., and Dr. Alexander W. Souter, Preoperative and Postoperative Use of Vitamin K (original work).  
Dr. Maurice O. Belson, Uterine Hemorrhage—Technic of Vaginal Packing.  
Dr. Roy J. Jeffernan, Myomectomy During Pregnancy—A Report of Four Cases.  
Dr. William C. Moloney, Erythroblastosis Foetalis.  
Dr. Louis E. Phaneuf, Use of Pessaries.

**New Dean at Boston University.**—Dr. Bennett F. Avery, associate professor of anatomy, American University of Beirut, Beirut, Syria, has been appointed dean of Boston University School of Medicine, Boston, succeeding the late Dr. Alexander S. Begg. Dr. Avery graduated at the University of Michigan Medical School, Ann Arbor, in 1925, serving as a Rockefeller Foundation fellow in the department of anatomy the following year. He was adjunct professor of anatomy at the University of Beirut from 1926 to 1929 and has been associate professor since 1930. During the year 1929-1930 he was a Rockefeller Foundation fellow at the University of Chicago. He served for a time as acting dean in Beirut. Dr. Avery was to take up his new work January 1.

### MICHIGAN

**Society News.**—Dr. Harther L. Keim, Detroit, discussed treatment of the more common dermatoses before the Jackson County Medical Society, Jackson, November 20.—Dr. Soma Weiss, Boston, lectured before the Wayne County Medical Society, Detroit, December 9, on "Types of Bright's Disease and Their Management."

**Hospital Day.**—The Woman's Hospital, Detroit, observed "Hospital Day," November 13, with the following program:

Dr. Catharine MacFarlane, Philadelphia, Report of an Experiment in the Control of Cancer of the Uterus.  
Dr. Arlie R. Barnes, Rochester, Minn., Significant Objectives in the Treatment of Congestive Heart Failure.  
Dr. Harry M. Kirschbaum, Detroit, Demonstration of Electroretinophony.  
Dr. Everett D. Plass, Iowa City, Hypertension in Obstetric Patients.  
Dr. Donald W. Gordon Murray, Toronto, Use of Heparin in Thrombosis, Embolism and Blood Vessel Surgery.

S. L. A. Marshall, Detroit, addressed the dinner session on "Can America Stay Out of the War?"

**Plans for Medical Center in Detroit.**—With the selection of a site, plans for the proposed \$100,000,000 medical center have definitely taken shape, it is announced. Fourteen and one half acres, privately owned, have been acquired for the center, which is to include sixteen buildings when completed. It is estimated that construction will take five years, but present plans call for the completion of one unit of the hospital and the medical science building by next fall. The entire project will be owned by the Detroit Board of Education. A group of Detroit physicians has already raised eight million dollars of the total.

### MINNESOTA

**Conference on Preparedness and Defense.**—The American Legion Conference on Preparedness and Defense Through Health Education, Physical Education and Recreation was held at St. Paul, December 21. Frank McCormick, director of athletics, University of Minnesota, opened the meeting discussing "The Purpose of the Conference and the Interest of

the American Legion in the Movement." Other speakers included:

Dr. Morris Fishbein, Chicago, Editor of *THE JOURNAL*, Health and National Defense.  
Mr. V. K. Brown, director of recreation, Chicago Park District, Recreation and National Defense.  
Carl L. Nordly, University of Minnesota, Physical Education and National Defense.  
V. D. Irwin, D.D.S., dental health director, Minnesota Department of Health, Dental Health and National Defense.  
Mr. G. Cullen Thomas, General Mills, Minneapolis, The Food Processor.  
Governor Harold E. Stassen addressed the meeting.

### MISSISSIPPI

**Changes in Health Officers.**—Dr. James M. Campbell, Morton, has been appointed health officer of Marion County. —Dr. Arthur P. Vandergrift Jr., formerly of Jackson, has been named director of the De Soto County health unit, succeeding Dr. John W. Evans Jr., Hernando; the latter left to take postgraduate work at Washington University School of Medicine, St. Louis.

**Society News.**—The Clarksdale and Six Counties Medical Society was addressed in Clarksdale recently by Drs. Wesley J. C. Wiemers on "Phrenic Nerve Operations"; Ray H. Biggs, "Pneumothorax Therapy"; Allen A. Lilienthal, "Extrapleural Pneumothorax"; John S. Harter, "Thoracoplasties and Other Operations," and Henry Boswell, "The Significance of the Collapse Therapy Program at the Mississippi State Sanatorium." All are from Sanatorium. —Dr. Leon H. Brevard, Deeson, discussed "Nutrition and Resistance to Disease in Everyday Practice" before the Coahoma County Medical Society and the Clarksdale Hospital medical staff recently.

### MISSOURI

**The Hodgen Lecture.**—Dr. Claude S. Beck, associate professor of surgery, Western Reserve University School of Medicine, Cleveland, will present the annual Hodgen Lecture before the St. Louis Medical Society, January 14, under the auspices of the St. Louis Surgical Society and the Medical Fund Society. His subject will be "Surgery of the Heart."

**Society News.**—A symposium on the present status of bacterial chemotherapy in pediatrics was presented before the St. Louis Medical Society, December 10, by Drs. Charles R. Anderson, Henry L. Barnett and Alexis F. Hartmann and Anne M. Perley, M.A. John Elliott, Sc.D., Salisbury, N. C., discussed "Indications for and the Use of Blood Plasma as a Substitute for Whole Blood" before the society, December 3. —The Kansas City Surgical Society was addressed, November 20, among others, by Drs. Eugene O. Parsons and Nelse F. Ockerblad on "Congenital Absence of Diaphragm" and "Tumor of the Adrenal Gland," respectively. —Dr. Lealdes M. Eaton, Rochester, Minn., discussed "Clinical and Experimental Studies on Spinal Fluid Headaches and Root Pains," November 20, before the Missouri-Kansas Neuropsychiatric Society, Kansas City. —Enrique E. Ecker, Ph.D., Cleveland, read a paper before the Jackson County Medical Society in Kansas City, December 20, on "Recent Progress in Immunity." —Dr. Maurice H. Severs, Madison, Wis., will present a "Review on Anesthesia with Late Advances" before the Kansas City Academy of Medicine, January 17.

### NEW JERSEY

**Discussion of Mental Deficiency.**—An institute was held at the North Jersey Training School, Little Falls, December 16, with a panel discussion on "Medical Aspects of Mental Deficiency" as a feature. Members of the panel were Drs. Edward J. Humphreys, Thiells, N. Y.; Ellen C. Potter of the state department of institutions and agencies, Trenton; Georges H. Lussier, Marlboro; Elizabeth Nesbitt, Totowa, and James Q. Atkinson, New Lisbon.

**Society News.**—Dr. Oliver L. Stringfield, Stamford, Conn., addressed the Essex County Medical Society, Newark, December 12, on "Factors Affecting Mortality Rates Among Premature Infants" and Dr. Leroy A. Wilkes, Trenton, executive officer of the Medical Society of New Jersey, discussed the functions of his office. —Dr. Douglas Quick, New York, addressed the Academy of Medicine of Northern New Jersey, December 19, on "Cancer of the Mouth." —Dr. Herbert T. Kelly, Philadelphia, addressed the Burlington County Medical Society, Moorestown, recently on vitamin deficiency disease with special reference to vitamin therapy. —Dr. Willis P. Haines, Ocean City, addressed the Medical Society of Cape May County, Cape May Court House, December 10, on medi-

cal preparedness. —Dr. Martin E. Rehfuess, Philadelphia, discussed "Gallbladder Disease and the General Practitioner" before the Camden County Medical Society, Camden, December 3. —Dr. Elliott P. Joslin, Boston, addressed the Hudson County Medical Society, Jersey City, December 3, on "The Renaissance of the Treatment of Diabetes." —Dr. Henry C. Falk, New York, discussed "Office Gynecology" at a meeting of the Bergen County Medical Society in Teaneck, December 10.

### NEW YORK

**Eastman Memorial Lecture.**—Dr. Herbert C. Clark, director of the Gorgas Memorial Laboratory, Panama, gave the Eastman Memorial Lecture at the University of Rochester School of Medicine and Dentistry, December 16. Dr. Clark's subject was "Modern Problems in the Control and Spread of Tropical Diseases."

**Dinner in Honor of State President.**—The Medical Society of the County of Monroe gave a dinner December 17 in Rochester in honor of Dr. James M. Flynn, Rochester, who is president of the Medical Society of the State of New York. Dr. Nathan B. Van Etten, New York, President of the American Medical Association, gave an address on "Medical Futures."

**Society News.**—Dr. Henry Jackson King, Binghamton, addressed the Broome County Medical Society, Binghamton, November 12, on "Treatment of Acute Appendicitis Complicated by Peritonitis—a Six Year Survey of Appendicitis." —Alexander O. Gettler, Ph.D., chief toxicologist of the medical examiner's office, New York, addressed the Ulster County Medical Society and the county bar association, Kingston, in October on "Chemistry in the Detection of Crime." —Dr. Frederick A. Collier, Ann Arbor, Mich., addressed the Medical Society of the County of Albany, November 27, on "Parenteral Feeding."

**Personal.**—Dr. Robert C. Woodman has retired as superintendent of Middletown State Homeopathic Hospital, Middletown. —Dr. August E. Witzel, Brooklyn, has been appointed superintendent of the Newark State School, succeeding Dr. Hiram G. Hubbell, who has been acting superintendent since the death of Dr. Charles L. Vaux. Dr. Hubbell returns to his former position as clinical director. —William D. Coolidge, Ph.D., director of the General Electric Research Laboratory at Schenectady, has been appointed a vice president of the General Electric Company. He will continue as director of research.

### New York City

**Medical College News.**—George W. Bachman, Ph.D., director of the School of Tropical Medicine of the University of Puerto Rico, under the auspices of Columbia University, addressed the staff and students of Long Island College of Medicine, December 18, on "Tropical Medicine: Its Historical Background and Its Importance in National Defense."

**New Medical Facilities for Steamship Line.**—A new eight room medical unit was opened by the Grace Line in November to care for its 2,000 seagoing and shore workers. The unit has a medical examination division, where each employee is examined prior to employment and periodically thereafter, and a first aid and dispensary division. Dr. William G. Terwilliger is medical director of the line. The staff includes two assistant physicians, five ship surgeons who serve on the vessels of the line, five ship nurses and three trained attendants.

**Personal.**—Alexander O. Gettler, Ph.D., received a Townsend Harris Medal at the sixtieth annual dinner of the Associated Alumni of the College of the City of New York, November 6. Dr. Gettler, professor of toxicology at New York University College of Medicine and city toxicologist, was cited as a "lecturer before learned societies, prolific writer in highly specialized fields of chemistry, shrewd investigator of the evidences of crime, and thereby an important helper and abettor of the work of those agencies of the city government devoted to the preservation of the public safety." An alumni service medal was awarded to Dr. Martin W. Ware, cited as "volunteer surgeon to the athletes of C. C. N. Y." for more than a decade.

**Museum of Health Has Permanent Home.**—The American Museum of Health, incorporated in 1937, will be permanently installed in the building formerly occupied by the Masterpieces of Art exhibit during the World's Fair, according to an agreement signed December 5 by Park Commissioner Robert Moses and Louis I. Dublin, Ph.D., chairman of the board of directors of the museum. The popular museum



devoted to medicine and public health will form an important unit in the civic, educational and recreational center being developed on the site of the fair. Its operation will be financed through public subscription of funds and through memberships, it was said. The American Museum of Health managed and operated the Medicine and Public Health Building at the World's Fair, which was visited by 11,800,000 persons during the two years. Many of the important exhibits from the Medicine and Public Health Building will form part of the museum's collection and many new exhibits are being created for it. Since its incorporation the museum has received financial support from the Carnegie Corporation of New York, the Josiah Macy Jr. Foundation, the Rockefeller Foundation, the John B. Pierce Foundation, nine large insurance companies and a number of pharmaceutical firms. Mr. George McAneny is president of the museum; Mr. Frederick Osborn, vice president, and Mr. Sam A. Lewisohn, treasurer. The directors include Mayor La Guardia, George E. Vincent, Ph.D., Dr. Dublin, Mr. James Marshall and Drs. John L. Rice, health commissioner, George Baehr, David J. Kaliski, Victor G. Heiser, Seth M. Milliken and Malcolm Goodridge. Homer N. Calver is director of the museum.

**Society News.**—A symposium on "Cancer of the Gastro-intestinal Tract" was presented at the first fall meeting of the International Spanish Speaking Association of Physicians, November 15, by Drs. Charles W. Mayo, Rochester, Minn.; Lester M. Morrison, Philadelphia, and Francis Carter Wood and Maurice Lenz. New branches of this society have recently been established in Los Angeles, New Orleans, Hollywood and San Antonio and in Skagway, Alaska.—A meeting of the New York Diabetes Association was held at the New York Academy of Medicine, December 13. Drs. Henry H. Faxon, Boston, and Frederick W. Williams discussed surgical and medical aspects, respectively, of "Infection and Gangrene in the Lower Extremity in Diabetes." There were also reports from St. Luke's, New York, Roosevelt and Lenox Hill hospitals.—At a scientific session of the committee on cardiac clinics of the New York Heart Association, November 26, papers were presented by Drs. Willis Fiske Evans on "Peripheral Blood Flow in Hyperthyroidism" and Arthur C. DeGraff, "Present Status of Treatment of Subacute Bacterial Endocarditis."—Kenneth N. Ogle, Ph.D., Hanover, N. H., and Dr. Sidney L. Olsho, Philadelphia, among others, addressed the New York Society for Clinical Ophthalmology, December 2, on "Induced Size Effect and Its Measurement" and "Prescriptions for Cataract and Other Strong Lenses" respectively.—A symposium on "Newer Knowledge of Liver Disease" was presented at the stated meeting of the New York Academy of Medicine, December 5, by Drs. Isidor S. Ravdin, Philadelphia; Alexander B. Gutman and Franklin M. Hanger Jr.—A symposium on chemotherapy formed the program of the Harlem Medical Association, December 4. The speakers were Drs. Harold T. Hyman, Whealan D. Sutliff, Rupert Franklin Carter, Emanuel Appelbaum, Jacob L. Maybaum and J. Sydney Ritter.—Speakers at a meeting of the New York Physical Therapy Society, December 4, were Dr. Paul H. Hoch, on "Electric Shock Therapy in Mental Disorders," and Josephine L. Rathbone, Ph.D., on (a) "The Need of Learning Relaxation: Description of Certain Cases Recently Referred" and (b) "Items Discovered by Draft Board Physicians: A Challenge to Physical Medicine and Physical Education."

#### NORTH CAROLINA

**District Meeting.**—Dr. Frederic M. Hanes, Durham, was the guest speaker at the annual meeting of the Seventh District Medical Society, November 20. An afternoon session was held in Kannapolis, with a clinic conducted by Dr. Hanes and addresses by Drs. Thomas C. Bost, Charlotte, on "Gunshot Wounds of the Pregnant Uterus"; Abner M. Cornwell, Lincolnton, "Traumatic Injuries of War and Peace"; Andrew Blair, Charlotte, "Nephrosis," and John Elliott, Sc.D., Salisbury, "Blood Plasma in the Treatment of the Sick Child." Following a banquet at the Hotel Concord in Concord, Dr. Hanes spoke on "Modern Concepts of Vitamin Therapy."

#### NORTH DAKOTA

**New Head of Preventable Diseases.**—Dr. Frank J. Hill, director of the Mason-Manistee-Benzie Health Department, Manistee, Mich., has been appointed director of the bureau of preventable diseases in the state department of health, according to the *Journal of the Michigan State Medical Society*

#### OHIO

**University of Cincinnati News.**—The Committee on Research in Dementia Praecox organized by the Scottish Rite Masons renewed its grant of \$1,000 to the University of Cincinnati College of Medicine for the second year and increased it by \$500, the college recently reported. The following promotions in the medical faculty were announced: Dr. Alphonse R. Vonderahe to associate professor of anatomy; Drs. John H. Skavlem and Leon Schiff, associate professors of medicine.

**Dr. Lavan Returns to Toledo.**—Dr. John L. Lavan, Grand Rapids, Mich., who was health commissioner of Toledo for four years before going to Michigan, has returned to Toledo to become director of a new public health district. Dr. Lavan left Toledo to be health officer of Kalamazoo, Mich., in 1932 and went to Grand Rapids as city health officer in 1935. He graduated from the University of Michigan Medical School in 1914. In 1939 Dr. Lavan was made secretary of the newly reorganized advisory council to the state department of health.

**Personal.**—Dr. Derrick T. Vail Jr., professor of ophthalmology, University of Cincinnati College of Medicine, Cincinnati, was recently appointed editor of the *American Journal of Ophthalmology*. He succeeds Dr. Lawrence T. Post, St. Louis, who resigned after having been editor since 1931.—Dr. Lloyd H. Gaston, director of the Sanilac County Health Department, Sandusky, Mich., has been named director of local health services in the Ohio Department of Health, according to the *Journal of the Michigan State Medical Society*.—Dr. Herman J. Nimitz has been named director of the Cincinnati Anti-Tuberculosis League to succeed the late Dr. Ray G. DeVoist.

**Society News.**—Dr. Samuel C. Harvey, New Haven, Conn., addressed the Academy of Medicine of Cleveland, December 20, on "Diet in Relation to Wound Healing."—Dr. Walter Estell Lee, Philadelphia, addressed the Summit County Medical Society, Akron, December 3, on "Systemic and Visceral Changes in Severe Burns."—Dr. Howard E. Boucher, Columbus, state selective service medical officer, addressed the Mahoning County Medical Society, Youngstown, December 17, on "Problems of the Examining Physician."—Dr. William D. Collier, Youngstown, addressed the Columbiana County Medical Society in Lisbon, December 10, on "Endocrine Pathology and Physiology—Emphasis on Practical Application."

#### PENNSYLVANIA

**Society News.**—Drs. John R. Simpson and Lucien A. Gregg, both of Pittsburgh, addressed the Westmoreland County Medical Society, Greensburg, December 17, on "Common Diseases of the Upper Respiratory Tract" and "Therapeutic and Dietary Management of the Pneumonia Patient" respectively.

#### Philadelphia

**Lecture by Professor Dam.**—Prof. Henrik Dam of the Biochemical Institute of the University of Copenhagen, Denmark, will give a lecture before the Philadelphia Academy of Surgery, January 13, on "Vitamin K, Its Role in Human Pathology and Its Application to Therapeutics."

**"Cyclotron Night."**—The meeting of the Philadelphia County Medical Society, January 15, will be devoted to study of the cyclotron, with Dr. John H. Lawrence, assistant professor of medicine, University of California Medical School, San Francisco, and Gaylord P. Hornwell, University of Pennsylvania, as the speakers, on "How the Products of the Cyclotron Are Applied in Medical Problems" and "How the Cyclotron Works" respectively.

#### Pittsburgh

**Society News.**—At the first fall meeting of the Pittsburgh Surgical Society, November 22, the speakers were Drs. Henry T. Price, on "The Acute Abdomen in Children"; Holland H. Donaldson, "Diagnosis of Acute Surgical Lesions of the Abdomen in Childhood," and Herbert Frankenstein, "Fat Embolism Following Trauma."—Speakers at a meeting of the Allegheny County Medical Society, December 17, were Drs. Andrew P. D'Zmura, on "Nondisabling Heart Conditions"; Joseph W. McMeans, "Anatomical Evaluation of the Symptoms of Syphilis of the Aorta"; Thomas Evans Jr., "Atypical Symptomatology in Ectopic Pregnancy," and John D. Singley, two papers, "Value of the Omentum in Abdominal Surgery, with Special Reference to the Free Omental Graft," and "Treatment of Operative Abdominal Incisions Without Dressings, with Results."

## SOUTH CAROLINA

**Founders' Day at Medical College.**—The Medical College of South Carolina, Charleston, celebrated its annual Founders' Day November 7. Clinics were held at Roper Hospital during the day and there was a banquet in the evening at the Fort Sumter Hotel with Dr. Louis Hamman, Baltimore, as the chief speaker on "Coronary Thrombosis."

**Officers Elected to Succeed Dr. Hines.**—Dr. Julian P. Price, Florence, was elected secretary and treasurer of the South Carolina Medical Association at a meeting of the council in Columbia, December 3, to succeed Dr. Edgar A. Hines, Seneca, who died November 27. Dr. Joseph I. Waring, Charleston, was elected editor of the state medical journal; Dr. William L. Pressly, Due West, state chairman for medical preparedness, and Dr. Thomas A. Pitts, Columbia, member of the House of Delegates of the American Medical Association, it is reported.

## TENNESSEE

**Society News.**—Dr. Eugene M. Regen, Nashville, addressed the Davidson County Medical Society, Nashville, December 10, on "Fractures and Fracture Dislocations of the Spine."

—Drs. Raphael Eustace Semmes and Robert Lyle Motley, Memphis, addressed the Madison County Medical Society, Jackson, November 5, on "Low Back Pain and Sciatica" and "Differential Diagnosis and Treatment of Angina Pectoris and Coronary Occlusion" respectively.

**State Health Meetings.**—Dr. Lloyd M. Graves, Memphis, was named president-elect of the Tennessee Public Health Association at its annual conference in Nashville, October 14-16, and Dr. John J. Lentz, Nashville, became president. Dr. Robert H. Hutcheson, Nashville, was reelected secretary. —Dr. Horton R. Casparis, Nashville, was reelected president of the Tennessee Tuberculosis Association at its annual meeting in Nashville in October. Dr. Stanford M. Herron, Jackson, is secretary and J. P. Kranz, Nashville, is executive secretary.

## TEXAS

**Postgraduate Assembly.**—The Taylor-Jones County Medical Society sponsored the West Texas Postgraduate Assembly in Abilene December 20 with Drs. George R. Herrmann, Galveston, and Edward William Alton Ochsner, New Orleans, as the guest speakers. Dr. Herrmann discussed procedure and methods in heart examinations; pyonephrosis, hypertension and convulsions; primary anemia, and sudden cardiovascular disturbances, recognition and management. Dr. Ochsner's subjects were peptic ulcer, intestinal obstruction, lung abscess, thrombophlebitis and phlebothrombosis. Dr. Neil D. Buie, Marlin, president-elect of the Texas State Medical Association, was the speaker at a banquet in the evening.

## VERMONT

**Personal.**—Dr. W. Scott Nay, Underhill, secretary of the state board of medical registration for thirty-six years, was honored with a community reception on his ninetieth birthday, December 12.—Dr. Horace G. Ripley, superintendent and physician in chief at Brattleboro Retreat, Brattleboro, has resigned, it is reported.

## VIRGINIA

**University News.**—The University of Virginia Department of Medicine in cooperation with the extension division presented the twenty-sixth Postgraduate Clinic recently, a symposium on obstetrics and gynecology. Among the speakers were Drs. Henry H. Hazen, U. S. Public Health Service, Washington, D. C., on "Syphilis in Pregnancy"; James R. McCord, Atlanta, Ga., "Puerperal Infections"; Herbert F. Traut, New York, "Pyelitis in Pregnancy," and Maurice B. Strauss, Boston, "Anemias of Pregnancy." Dr. Robert D. Mussey, Rochester, Minn., gave the James Carroll Flippin Lecture on "The Toxemias of Pregnancy."

**Changes in Public Health Personnel.**—Dr. Walter Brownley Foster, head of the Richmond department of public welfare for sixteen years, has been appointed to the staff of the state department of health.—A new health district consisting of Isle of Wight, Nansemond, Norfolk and Princess Anne counties has been formed with Dr. John C. Neale Jr., Abingdon, in charge and headquarters at Norfolk. Dr. Neale was succeeded by Dr. Harold M. Kelso as director of the Southwest district with headquarters at Abingdon, and Dr.

Allen W. Lane, Lawrenceville, has been appointed health officer of Pulaski County to succeed Dr. Kelso. Dr. Thomas F. McGough Jr., recently assistant health officer of Pulaski County in Pulaski, has been transferred to Northampton County with headquarters in Eastville to replace Dr. William Y. Garrett, who will take a course at the Johns Hopkins School of Hygiene and Public Health, Baltimore.

## WASHINGTON

**Seminar at Seattle Hospital.**—Dr. Frank L. Horsfall Jr., New York, conducted a seminar in internal medicine at the Seattle General Hospital, December 26-28. The subjects of his lectures were virus diseases, virus pneumonias, specific therapy, influenza, bacterial pneumonias and specific prophylaxis. Dr. Horsfall addressed a special meeting of the King County Medical Society, December 26, on "Chemotherapy" and gave an address at the hospital staff dinner, December 27, on "The Periphery of Medical Research."

## PHILIPPINE ISLANDS

**Society News.**—At a meeting of the Manila Medical Society, September 10, the speakers included Drs. Jesus Pempengco and Natalio Santiago, Calocan, on "Pregnancy and Collapse Therapy in Pulmonary Tuberculosis: Observations on 108 Cases"; Carmelo P. Jacinto and Manuel T. Laboz, Calocan, "Clinicoröntgenographic Recognition of Massive Pulmonary Atelectasis."

## PUERTO RICO

**Society News.**—Dr. Eugene L. Opie, New York, addressed a meeting of the Medical Association of San Juan and the Society of Tuberculosis Physicians of Puerto Rico, November 16-17, on "Frequency and Spread of Tuberculosis" and "Infection and Reinfection with Tuberculosis." The tuberculosis society conferred a medal on Dr. Opie for "distinguished services in the field."

**Hospital News.**—Admiral William D. Leahy, governor of Puerto Rico, laid the cornerstone, November 16, for an addition to the Preventorium for Tuberculous Children at Guaynabo. Speakers at the ceremony, in addition to Admiral Leahy, were Drs. Ezequiel Martinez-Rivera, Oscar G. Costa-Mandry, Eduardo Garrido Morales, Jacobo Simonet, San Juan, Eugene L. Opie, New York, and Mr. Rupert Emerson, director of the division of territories and island possessions of the U. S. Department of the Interior.

**Venereal Disease Control Intensified.**—The Puerto Rico Department of Health has intensified its program for the control of venereal diseases, especially gonorrhea, to meet problems resulting from increased concentration of military forces. More clinics have been opened and some clinic sessions are being reserved for attention to the control of gonorrhea in towns near which military forces are stationed. An efficient system of case reporting has been put into practice and diagnostic laboratory services are available without charge to all physicians. In addition, free drugs will be provided on request to all clinics and physicians, according to a report in the *Puerto Rico Health Bulletin*. Follow-up workers are to be provided to locate and return to treatment all patients who lapse from treatment before they are cured.

## GENERAL

**Days of Observances.**—The fifth annual Social Hygiene Day has been set for February 5 by the American Social Hygiene Association. Emphasis in the 1941 observance will be on national defense.—The National Child Labor Committee announces that the annual Child Labor Day will be observed during the week-end of January 25-27.

**Van Meter Prize Competition.**—The American Association for the Study of Goiter again offers the Van Meter Prize Award of \$300 and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The essays may cover either clinical or research investigations, should not exceed 3,000 words in length, must be presented in English and a typewritten double spaced copy must be sent to the corresponding secretary of the association, Dr. W. Blair Mosser, 133 Biddle Street, Kane, Pa. The award will be made at the annual meeting in Boston, May 26-28, and a place reserved on the program for the author if it is possible for him to attend. The essay will be published in the annual proceedings of the association, but this will not prevent its further publication in any journal selected by the author, it was stated.

**Vital Statistics from the 1940 Census.**—The division of vital statistics of the Bureau of the Census is beginning an extensive program of special studies of data from the sixteenth decennial census, according to *The Registrar*, the official news bulletin of the bureau. The studies will appraise the accuracy and completeness of vital statistics data and analyze their social implications whenever possible, it was said. Subjects of the studies are the following: mortality from diseases of the heart, completeness of birth registration, results and problems of residence allocation of births and deaths, birth and death rates, urban-rural differences in mortality and natality, marriage and divorce statistics, differentials in judicial and penal treatment of offenders, distribution and characteristics of patients in mental institutions, medical care of patients in institutions and comparability of mortality statistics.

**Conference on Electrical Aids to Medicine.**—The committee on basic sciences of the American Institute of Electrical Engineers is arranging a conference on "New Electrical Aids to Biological and Medical Research" at the annual meeting of the institute in Philadelphia, January 29. Technical papers are to be presented by physicists with discussions by physicians. The speakers will be:

Robley D. Evans, Ph.D., associate professor of physics, Massachusetts Institute of Technology, Cambridge, Mass., The Cyclotron.  
Albert Prebus, Ohio State University, Columbus, The Electron Microscope.  
John G. Trump, Sc.D., Massachusetts Institute of Technology, Cambridge, High Voltage X-Ray Sources.

Physicians who will discuss the papers will include Drs. Francis Carter Wood, New York, and Richard Dresser, Boston.

**Meeting on Industrial Medicine.**—The annual winter clinical session of the Central States Society of Industrial Medicine and Surgery was held at St. Luke's Hospital, Chicago, December 6. The speakers included:

Dr. Fremont A. Chandler, Chicago, Spondylolisthesis.  
Dr. Roland P. Mackay, Chicago, Mental Conditions Associated with Trauma.  
Dr. Wesley A. Gustafson, Chicago, Spinal Cord Injuries.  
Dr. Will F. Lyon, Chicago, Hernia in Industry.  
Dr. George L. Apfelbach, Chicago, Causes of Impaired Union in Fractured Hips.  
Dr. Harry Culver, Chicago, Traumatic Lesions of the Genito-Urinary Tract.  
Dr. Cleveland J. White, Chicago, Industrial Dermatitis, Their Diagnosis, Scope and Prevention.  
Drs. Oscar A. Sander, Milwaukee, and Harold E. Davis, Chicago, The Silicosis Problem After Eight Years of Medical and Engineering Control.  
Dr. James A. Jackson, Madison, Wis., Open Reduction Treatment of Fractures.

Dr. Clay Ray Murray, New York, guest speaker at the evening session, discussed "Correlation Between Fracture Treatment and Fracture Pathology."

**Health of the Migratory Indigent.**—The U. S. Public Health Service recently made a study of the health of transients, variously estimated at from two hundred thousand to a million persons, and presented recommendations for solution of the medical problems involved in caring for them. Difficulties facing these people are especially urgent in view of the fact that almost two-thirds of the agencies giving medical care to transients restrict care to emergency or selected cases, the report said. Transients have more disabling illness than residents, it was found. As a result of the grossly poor living conditions, typhoid and dysentery have a high incidence and malnutrition appears to be common. Migration and transiency must be recognized as permanent characteristics of American life, the study concluded, and an organization of federal level should be created to direct and influence it. Medical care should be provided for all needy persons, regardless of residence, through planned cooperation of state and federal governments, it was recommended, with administration of the program centered in the local agency responsible for care of needy residents. Finally, particular concentration of transients in a state should be considered a special health problem in the allotment of federal funds for the maintenance and improvement of local public health facilities, the report concluded.

**Special Society Elections.**—Dr. Leon J. Menville, New Orleans, was named president-elect of the Radiological Society of North America at the annual meeting in Cleveland in December, and Dr. William Walter Wasson, Denver, was installed as president. Vice presidents elected were Drs. William E. Costolow, Los Angeles; Orion O. Feaster, St. Petersburg, Fla., and David S. Beilin, Chicago. Dr. Donald S. Childs, Syracuse, N. Y., was reelected secretary.—Marshall A. Barber, Ph.D., New York, was elected president of the American Academy of Tropical Medicine at the recent annual

meeting in Louisville, Ky.; Dr. Herbert C. Clark, Panama, R. P., vice president, and Ernest Carroll Faust, Ph.D., New Orleans, secretary.—Dr. Charles A. Thomas, Tucson, Ariz., was named president-elect of the Southwestern Medical Association at its annual meeting in Tucson in November, and Dr. William H. Woolston, Albuquerque, N. M., was installed as president. Drs. Kevin D. Lynch, El Paso, and James W. Hannett, Albuquerque, were elected vice presidents and Dr. Louis W. Breck, El Paso, secretary. The next annual meeting will be in El Paso. Dr. Franklin H. Maury, Tucson, was elected president of the Southwest Academy of Eye, Ear, Nose and Throat, which met at the same time, and Dr. Archie E. Cruthirds, Phoenix, Ariz., secretary.—Dr. Henry Franklin Carman, Dallas, Texas, was elected president of the Southern Tuberculosis Conference at its annual meeting in Monroe, La., in October. Mr. J. P. Kranz, executive secretary of the Tennessee Tuberculosis Association, Nashville, Tenn., was elected secretary.

## CANADA

**Society News.**—Dr. Waltman Walters, Rochester, Minn., addressed the Academy of Medicine of Toronto, December 3, at a meeting with the eleventh district of the Ontario Medical Association on "Lesions of the Biliary Tract."

**New Director of Connaught Laboratories.**—Dr. Robert D. Defries, associate director of Connaught Laboratories, University of Toronto, since 1917, has been appointed director to succeed the late Dr. John G. FitzGerald. Dr. Defries took his medical degree from the University of Toronto Faculty of Medicine in 1913 and joined the staff of the laboratory in 1915. He has been professor of hygiene and epidemiology and head of the department of epidemiology and biometrics since 1930 and associate director of the school of hygiene since 1925.

## LATIN AMERICA

**New Society of Urology.**—Formation of the Venezuelan Urological Association at a meeting in Caracas was recently announced. Dr. Alfredo Borjas was elected president; Dr. L. Rodriguez, vice president, and Dr. Leopoldo E. Lopez, secretary. The society is planning the first Venezuelan Congress of Urology to be held in Caracas in May.

**Pan American Congress of Endocrinology.**—The second Pan American Congress of Endocrinology will be held in Montevideo, Uruguay, March 5-8. The following sections are being organized: medicine, pediatrics, cardiology, psychiatry, odontology, surgery, urology, obstetrics and gynecology, physiology, histology and pathologic anatomy, biology, therapeutics, radiology and a medicosocial section. Dr. Juan C. Mussio-Fournier, Montevideo, is president of the congress and Dr. Pedro A. Barcia, Montevideo, is secretary. The official topics and those in charge of them are as follows:

Dr. Bernardo A. Houssay, Buenos Aires, Regulation of the Endocrine Function of the Pancreas.  
Prof. Alejandro Lipschütz, Santiago, Chile, Endocrine Basis of the Origin of Tumors of the Female Genital Organs.  
Prof. Mariano R. Castex and Dr. Mario Scheingart, Buenos Aires, Present Status of Hormone Therapy in Genital Disorders.  
Prof. Mussio-Fournier and Drs. J. M. Cerviño and Juan J. Bazzano, Montevideo, Cardiovascular System in Thyroid Insufficiency.  
Prof. Emilio Mira y Lopez, Habana, Cuba, Present Concept of the Endocrine Psychoses.  
Prof. Alberto Peralta Ramos, Buenos Aires, Endocrine Correlation in Disorders of the Genital Cycle.  
Prof. Clemente Estable, Montevideo, Relationships of the Endocrine Glands to the Eyes.  
Prof. L. Fraenkel and Drs. J. C. Barsantini and W. Buño, Montevideo, The Mammary Gland and the Endocrine Glands: Neurohumoral Interrelationships.  
Fred C. Koch, Ph.D., Chicago, Excretion and Metabolism of the Male Sex Hormone in Normal and Pathologic Conditions.  
Dr. Thales Martins, Rio de Janeiro, Recent Advances in Knowledge of the Biologic Activity of the Male Hormone.  
Dr. Herbert M. Evans, Berkeley, Calif., Present Knowledge of the Hormones of the Anterior Hypophysis.  
Prof. Carlos Foà, São Paulo, Biologic and Chemical Methods in the Service of Endocrinologic Diagnosis.

Information may be obtained by addressing II Congreso Pan-Americano de Endocrinología, Casilla de Correos 255, Montevideo, Uruguay.

**Hospital Honors Harvey Cushing.**—Salvador Hospital, Santiago, Chile, dedicated a new wing in honor of the late Dr. Harvey Cushing of Boston, November 7. A full length portrait of Dr. Cushing was unveiled by United States Ambassador Claude G. Bowers. The president of Chile, the minister of health and other officials were present, the *New York Times* reported.

**Dr. Clark Receives Walter Reed Medal.**—Dr. Herbert C. Clark, director of the Gorgas Memorial Laboratory of Tropical and Preventive Medicine, Panama, R. P., received the Wal-

ter Reed Medal of the American Society of Tropical Medicine at the annual meeting in Louisville, Ky., in November, in recognition of his years of work in the eradication of malaria and other tropical diseases. Dr. Clark, a native of Indiana, graduated from the University of Pennsylvania School of Medicine in 1906. He served as pathologist of the laboratory of the board of health at Ancon, C. Z., from 1909 to 1922 and was later with the United Fruit Company for several years. He became director of the Gorgas laboratory in 1929.

### FOREIGN

**Society News.**—The French Red Cross has recently been reorganized by the union of three separate societies formerly in existence, the Red Cross *Courier* reports. Dr. Pasteur Vallery-Radot has accepted the presidency.

**Alien Physicians May Practice in Australia.**—The West Australian parliament recently passed a bill permitting qualified alien physicians to practice in certain country districts inadequately supplied with medical service. These districts are to be declared areas for regional registration. Sixteen centers in West Australia are said to be without physicians, owing to enlistments in the army. A hospital may be similarly designated and registration confined to the hospital. After holding registration for seven years for a regional area a physician may be registered throughout the state, according to a dispatch from the Australian Associated Press. The alien has the right of appeal against a medical board's refusal to register. New South Wales, Queensland and South Australia permit registration of alien physicians who have completed a shortened course at an Australian university, but Victoria does not, the dispatch says.

### Deaths in Other Countries

Dr. Charles William Mansell-Moullin, examiner in surgery at the universities of Oxford, Cambridge and Glasgow and author of works on ulcer of the stomach and on tumors, died in London, November 10, aged 89.—Dr. Anton Schnöller, Davos, Switzerland, tuberculosis specialist, said to have been one of the first physicians to practice the pneumothorax treatment, died in Zurich, November 3, aged 75.—Dr. Adolpho Lutz, for many years chief of the department of medical zoology at the Instituto Oswaldo Cruz, Rio de Janeiro, died, October 6, aged 84. According to "Who's Who in Latin America," Dr. Lutz was at one time director of a leper colony in Hawaii and later director of the bacteriologic institute of the state of São Paulo. In the latter capacity he demonstrated by experiments on himself that yellow fever was transmitted by the *Stegomyia* mosquito, organized a campaign and eradicated the disease from the state.—Dr. Desiré Glibert, one of the leading men in industrial hygiene in Europe, died in Belgium, October 15, aged 81. He entered the new field of factory inspection in Belgium with its foundation in 1895, became chief inspector and in 1919 created an independent department for medical survey of industrial plants, of which he was head up to 1929. He was president of the international permanent committee for research on occupational diseases. Glibert published investigations on mercury poisoning and silicosis, but his lasting merit is in medical factory inspection, the protection of workers and the compensation for occupational diseases in Belgium.

### CORRECTION

**Control of Venereal Diseases in Argentina.**—In the Buenos Aires letter in THE JOURNAL, Nov. 16, 1940, page 1736, the figure in the fifth line in the second column at the top of the page should have been 0.49 per cent instead of 49 per cent.

## Government Services

### Changes of Station in U. S. Public Health Service

Passed Asst. Surg. Wilson T. Sowder has been relieved at Morristown, Tenn., and ordered to Pensacola, Fla., to establish headquarters and Passed Asst. Surg. Charles S. Sample Jr. has been relieved at Springfield, Mo., and assigned as chief medical officer at the federal reformatory at El Reno, Okla.

### Division of Chemotherapy in National Institute of Health

The U. S. Public Health Service announces the formation of a new division of chemotherapy in the National Institute of Health to be under the direction of Dr. William H. Sebrell Jr. The new unit will be concerned with research on sulfanilamide products, new synthetic drugs with antimalarial properties to make the United States independent of the Dutch East Indies supply of quinine, new synthetic drugs to supplement the supplies of opiates and studies relating to aging and nutrition. The chemotherapy division will have quarters at the National Institute of Health in Bethesda, Md., in a laboratory building now being equipped. The building will also be the headquarters of the divisions of chemistry and zoology.

### Positions Open for Dental Workers

The U. S. Civil Service Commission announces vacancies for dental workers in the U. S. Public Health Service, Federal Security Agency, Veterans Administration and the War Department. The positions are dental laboratory mechanic, salary \$2,000; assistant dental laboratory mechanic, salary \$1,440, and dental hygienist, salary \$1,620. Applications will be accepted at the commission's Washington office not later than February 3 if received from states east of Colorado and not later than February 6 if received from Colorado and states westward. Applicants must have completed at least fourteen units of high school study; otherwise, they must pass a written test. All will be rated on their education and experience as shown by their applications and corroborative evidence. Further information and application blanks may be obtained from the Secretary of the Board of U. S. Civil Service Examiners at any first or second class post office or from the commission at Washington, D. C.

### Examination for Appointment to Public Health Service

The U. S. Public Health Service announces an examination for appointment in the commissioned corps in the grade of assistant surgeon (medical only). Applicants must not have passed their thirty-second birthday on the date the examination is taken, must be citizens of the United States, graduates of a recognized medical college and must have completed by July 1 next at least one year of internship or its equivalent. The compensation for this grade is \$3,158 per annum with dependents and \$2,699 without dependents. Candidates should arrange to have their physical examinations and prepare their autobiographies before presenting themselves at any one of the following places, where the board of examiners will be on the dates given:

U. S. Marine Hospital, Boston, January 13.  
U. S. Marine Hospital, Staten Island, N. Y., January 14.  
U. S. P. H. S. Building, Washington, D. C., January 16.  
U. S. Marine Hospital, Baltimore, January 17.  
U. S. Marine Hospital, Norfolk, Va., January 18.  
U. S. Marine Hospital, Chicago, January 20.  
U. S. Marine Hospital, Seattle, January 24.  
U. S. Marine Hospital, San Francisco, January 27.  
U. S. P. H. S. Relief Station, Los Angeles, February 3.  
U. S. Marine Hospital, St. Louis, February 7.  
U. S. Marine Hospital, Cleveland, February 11.  
U. S. Marine Hospital, Galveston, Texas, February 14.  
U. S. Marine Hospital, New Orleans, February 15.  
U. S. P. H. S. Relief Station, 365 Federal Building, Miami, Fla., February 19.

Those who complete the physical examination and certain other parts of the examination will be allowed to take the written examination beginning February 24 either at the place where the physical examination was conducted or at some other nearer point; or candidates may elect to go to Washington, D. C., to take the entire examination. The written and clinical portions of the examination will consume about three days. Travel expenses must be paid by the applicants. Application blanks may be obtained by writing to the Surgeon General, U. S. Public Health Service, Washington, D. C. The forms may be filled out and delivered personally to the board of examiners or blanks may be had from the board at the time the applicant appears for examination. Applicants will be required to present their diplomas and evidence of United States citizenship to the board. Diplomates of the National Board of Medical Examiners are required to present their certificates to the board.

## Foreign Letters

### LONDON

(From Our Regular Correspondent)

Nov. 30, 1940.

#### The Bombing of London Hospitals

The bombing of two of the great London hospitals—the London and St. Thomas's—has been described in previous letters. St. Thomas's has had to be evacuated. What occurred there has been reported in the *Lancet* by a correspondent, who is a member of the staff. He came by taxicab one morning and found the way near the hospital blocked by masses of fallen masonry, so that he had to get out and walk. His colleagues who had spent the night at the hospital looked somewhat shaken, which was not surprising, for their windows had been blown in and their beds covered with glass and with plaster from the ceiling. Desperate efforts were made to rescue those buried under the fallen masonry. It was hoped to save at least one alive, but when the tunnelers reached a woman after several hours' dangerous work she died before she could be extricated. During the night the bombing continued. One ward was occupied by 25 gynecologic patients, most of whom had undergone operation within a few days. Every bed was covered with glass, but not a patient had been scratched. The nurses removed the glass-covered blankets and put new ones on every patient. When rescuers arrived the patients were all singing in the dark. There was no option but to evacuate all the patients from the hospital. During the afternoon by strenuous effort of the engineering staff more water and electric power became available. The staff and governors unanimously decided to reopen the hospital by improvising wards in the basement and strengthening those on the ground floor.

By the following week two hundred and six beds were made available. While some members of the staff were in their room near the center of the hospital, the sirens sounded and they went downstairs to take up their places in the central hall, which had been planned as a receiving room for casualties. While four or five of the staff were sitting on a bench they suddenly saw a vast sheet of flame accompanied by a devastating explosion. Those who were not blown off the bench sat huddled waiting for the roof to fall on them. Large missiles hurtled all round, but nobody was touched. For a moment or two there was silence, then a babel of talking and shouting. A woman's voice said plaintively "I don't think I am going to like this at all." Torches were flashed but were almost useless in the dust and mirk. A voice shouted "Go carefully—there may be no floor." Carefully made plans had been wrecked in a moment. The reception room was devastated, the operating room wrecked. Already men were bringing in casualties and asking where to put them, and for a time nobody knew. Difficulties were increased by the darkness; one could not find one's colleagues, but in a remarkably short time order was restored. Members of the staff went into the wrecked operating room and grabbed everything they could find, carrying it out on stretchers, trays and tables and in their pockets. Within an hour a new operating room had been improvised at the other end of the hospital, and a surgical team complete with overalls and masks was operating.

The London Hospital is the largest of the voluntary hospitals of the metropolis and covers  $9\frac{1}{2}$  acres. In the board room is a large map marked with colored circles, each bearing a date, which is that when a bomb fell on that spot. Twenty-one bombs—incendiary, high explosive and of small caliber—have hit the hospital. Ten thousand panes of glass have been broken. Nevertheless three hundred beds, about a third of the normal for the hospital, are in use. There is also a large first aid post.

The work of the hospital is all conducted on the first, ground and lower ground floors. The hospital has its own squad of fire fighters, who have been able to reduce the damage which otherwise might have been done. The medical college has been badly damaged and the top floor of the nurses' home has been struck by an incendiary bomb, but the rest of the building was saved because the floor was of stone. The wards and administrative offices of the hospital are all shored up. There are now in use two hundred casualty beds and one hundred for the civilian sick, the hospital having otherwise been evacuated according to the scheme explained in previous letters. The hospital population is kept on the move; as soon as patients can be transported they are sent to the safer "sector" hospitals. Thus beds are always available for emergencies.

#### The Hygiene of Air Raid Shelters

The large number of persons who spend the night in air raid shelters has produced a serious sanitary problem. In London a hundred thousand persons sleep at night on the platforms and passages of the tube railways—a use for which they were never intended. The government appointed a committee under the chairmanship of Lord Horder to investigate the sanitary conditions of the London shelters and make recommendations. It reports that the evacuation from London of four hundred and eighty-nine thousand school children, 56 per cent of the whole, as well as the transfer to hospitals of the emergency medical service in the country of four thousand aged and infirm persons who frequented the shelters, was a help. The committee recommended the appointment of whole time shelter marshals and the provision of adequate sanitary accommodations. In every shelter for more than five hundred people there should be a first aid post and a sick bay, and a physician should be in residence during the night or available at call. Beds and bunks should be allotted to the medical post at the rate of two beds and three tier bunks for every five thousand persons. At first the ordinary standards of ventilation could not be fulfilled. But until the present overcrowding is eased a standard 50 cubic feet per person should be followed. A dominant factor in the air pollution of shelters is the presence of closets. It is recommended that wherever possible the men's closets should be placed outside the shelters. The risk of air-borne infection should be reduced by spraying with solution of sodium hypochlorite.

A committee of architects, engineers, scientists and physicians under the chairmanship of Prof. J. B. S. Haldane advocates the universal provision of deep shelters. So far only surface shelters of brick or corrugated iron have been provided in most places. They protect against blast or bomb fragments but not against a direct hit and therefore are regarded as inadequate. The committee advocates bomb proof shelters of reinforced concrete and also increased underground accommodation by extension of the tunnels of the London underground railways.

#### The Employment in Hospitals of Alien Physicians and Nurses

The large number of aliens from enemy countries has presented the government with a difficult problem. They are usually refugees from persecution, but there is always the possibility that enemies may be among them. Therefore the government has interned large numbers as a measure of safety, but this has been an injustice to many, who on further inquiry have been released. Hospitals were prohibited from employing persons of enemy nationality. This prohibition has now been withdrawn in districts outside the protected areas (areas in which there is special danger from enemy action). In the nonprotected areas persons of German, Austrian and Italian nationality may be employed as physicians, medical students or nurses subject to the following conditions: 1. In the event of invasion or other

serious military situation, which would make it necessary for the military authorities to take full control of the area, they may find it necessary to order the immediate removal from the hospital of the persons in question. 2. Every effort should be made to segregate military or naval patients in separate wards, in which the aliens must not be employed. 3. Wherever practicable alien physicians and nurses should be employed only in wards where British physicians also are engaged. 4. The number of aliens of enemy nationality who may be employed in a hospital must be limited in relation to the total staff. For this purpose account should be taken of the following categories: physicians, nurses, other professional and technical workers, students. Within any of these categories not more than 10 per cent of the personnel (or 20 per cent in the case of hospitals of less than one hundred beds) may be aliens of enemy nationality. Permits from the Aliens War Service Department will be required before an alien can be employed.

### Ample Supplies of Essential Foods

Though we are rationed for some important foods such as meat, fats, butter and sugar, other food supplies are ample, thanks to maintenance of imports and increase of home production. The country is unlikely to suffer from any lack of essential food supplies in the second winter of the war. In framing its policy the government has followed the advice of scientists on relative food values. The whole scheme of production from our own soil and food importation is related to a basic diet which will most economically support a healthy population. Any necessary temporary reduction in imports due to the need for cargo space to carry munitions of war will be in less essential foodstuffs. It has just been decided that bananas are not essential and that their importation must stop. This decision has provoked protest from the fruit trade, which points out that it will be difficult for the public to follow the Ministry of Food's advice to eat fresh fruit. In normal times bananas represent more than a fifth of our total fruit consumption. Coming after the loss of American apples and pears and the curtailment of orange, lemon and onion imports, it is claimed that fruit imports will be reduced to a third of their prewar figure. One result will be an increase in the retail price of vegetables as the only way of meeting fixed overhead charges. Prewar imports of bananas amounted to 300,000 tons annually. The plans for stimulating home production are all directed to increasing the supply of essential foods and checking production of luxuries. Priority is given to milk, potatoes, bread and vegetables. The standardization of certain foodstuffs, such as margarine, is being pressed forward. Some essential foods, such as bread, are subsidized so as to keep the price down for those of limited means.

On the recommendation of the Food Rationing Committee of the Medical Research Council, appointed to advise as to the necessity for modifying the allowance in certain cases, the following additions have been authorized by the minister of food: In diabetes mellitus one extra ration of meat and two extra rations of butter and margarine each week. In spontaneous hypoglycemia two extra-rations of sugar a week. In steatorrhea (celiac disease, celiac infantilism and tropical sprue) three extra rations of meat each week in exchange for the butter-margarine ration. The present ration of sugar in ordinary cases is 8 ounces a week, of butter 4 ounces and of margarine 2 ounces.

### Compensation for Byssinosis

A bill has passed through parliament granting compensation to workmen for byssinosis (disease due to inhalation of fine particles of cotton dust which penetrate deeply into the lungs, producing chronic bronchitis complicated by emphysema and in some cases by asthma) after not less than twenty years in dusty processes of the cotton industry. The disease is prevalent among

operatives in cotton rooms, cotton blowing rooms and card rooms. The bill applies only to males, as it is caused by heavier process in cotton mills on which women are not employed. The disease was not previously scheduled under the workmen's compensation act because in many cases the diagnosis was so difficult that the general practitioner or even the factory examining surgeon could not be certain that it was occupational in the case of a particular man. A committee was therefore set up by the government, which reported that when there was total incapacity after not less than twenty years' employment in the industry a medical board should be able, after considering the industrial history as well as the medical evidence, to decide whether the disease was occupational. A scheme is to be followed within the workmen's compensation act on the lines of the schemes already followed for silicosis and asbestosis.

### Home Food Supplies

In the House of Commons the minister of agriculture gave a reassuring picture of the increased contribution to our national food supply which is being made at home. The plowing of two million additional acres is a great gain and the number of cattle, particularly dairy cattle, has been increased. We enter the second winter of the war with considerably increased meat reserves. British agriculture is in a well balanced condition and well able to face the demands which next year's campaign may make on food production. It is the policy of the government that milk production must come first. Although milk production decreased as a result of last year's hard winter, there is good reason to hope for an improvement this winter. The aim of the government is to secure the maximum of food production necessary to maintain the health of the nation in wartime. Much attention is being given to nutrition. Experts whose advice has been sought agree in putting among the vital requirements bread, milk, potatoes, oatmeal, vegetables and fats. Meat does not fall within this category but is admitted to be desirable, if only because regard must be paid to the habits of the people and the foodstuffs they like.

## Marriages

WILLIAM PROVINCE MCGUIRE, Winchester, Va., to Miss Dorothy Elizabeth Robinson of Paterson, N. J., in October 1940.

CHARLES S. NORBURN, Asheville, N. C., to Miss Helen Sophia Johnson at Merryvale, Tenn., in November 1940.

IRVING E. SCHIEK JR., Rhinelander, Wis., to Miss Mary Margaret Hughes of Milwaukee, Sept. 21, 1940.

JOHN KENNETH KARR, Milwaukee, to Miss Mary Caroline Ielmini of Bessemer, Mich., Aug. 17, 1940.

THOMAS NORWOOD LIDE, Washington, D. C., to Miss Janet Ormond of Durham, N. C., Oct. 12, 1940.

ARNOLD E. NAEGELI, St. Paul, to Miss Audrey Elinor Miller at Toronto, Ont., Canada, Oct. 31, 1940.

CLARENCE JOSEPH KURTH, Council Bluffs, Iowa, to Miss Jean Burke of Omaha, Sept. 14, 1940.

JOSEPH PANCOAST REATH, St. Davids, Pa., to Miss Sarah Ann Mitchell of Wayne, Nov. 23, 1940.

FREDERICK J. STODDARD to Miss Annette E. Dods, both of Ann Arbor, Mich., Sept. 7, 1940.

LOREN E. COLLINS, Estherville, Iowa, to Miss Ida Lieber of Spearfish, S. D., Aug. 27, 1940.

JEFF J. BAGGETT to Miss Frances Gose, both of Prairie Grove, Ark., Oct. 26, 1940.

ELMER C. PAULSON, Dalton, Minn., to Miss Ethel Mobraaten of Virginia, Aug. 3, 1940.

ABNER BURESH to Miss Jean Cray, both of Lime Springs, Iowa, Nov. 28, 1940.



## Deaths

**Thomas Shepard Southworth** ☉ New York; College of Physicians and Surgeons, medical department of Columbia College, New York, 1887; an Affiliate Fellow of the American Medical Association; member of the American Pediatric Society and president in 1920; secretary of the Section on Diseases of Children of the American Medical Association 1902-1903 and chairman, 1908-1909, and member of the House of Delegates in 1907; formerly consulting physician to the New York Nursery and Child's Hospital and the New York City Children's Hospital; aged 79; died, Nov. 14, 1940, in the Columbia-Presbyterian Medical Center of cerebral hemorrhage.

**Richard Schillinger** ☉ Richmond, Ind.; Miami Medical College, Cincinnati, 1894; past president of the Wayne County Medical Society; for many years member of the board of health; formerly mayor; for many years president of the staff of the Reid Memorial Hospital and chairman of the executive committee; president of the county pension examiners' board; medical superintendent of the Richmond State Hospital; aged 69; died, Nov. 21, 1940, in the Good Samaritan Hospital, Cincinnati, of cerebral hemorrhage.

**Melvin Harvey Walker Jr.** ☉ Pittsfield, Mass.; Harvard Medical School, Boston, 1915; fellow of the American College of Surgeons; served during the World War; was a member of the city board of health for many years; visiting surgeon, House of Mercy Hospital, Pittsfield, and Fairview Hospital, Great Barrington; on the associate staff of St. Luke's Hospital; aged 54; died, Nov. 21, 1940, of coronary thrombosis.

**Norman Leslie Rowe**, Jersey City, N. J.; Columbia University College of Physicians and Surgeons, New York, 1900; member of the Medical Society of New Jersey; physician in the public schools for many years; served during the World War; formerly member of the city board of health; on the staff of the Fairmount Hospital; aged 63; died, Nov. 30, 1940, in the Medical Center of Jersey City of carcinoma.

**David Collins Roach**, Burlington, Ill.; Northwestern University Medical School, Chicago, 1894; member of the Illinois State Medical Society; mayor of Burlington; for many years bank president; served during the World War; aged 69; on the staff of St. Joseph Hospital, Elgin, where he died, Nov. 18, 1940, of hypertension, nephritis and chronic myocarditis.

**Theodore Frederic Myler** ☉ Xenia, Ohio; University of Pennsylvania School of Medicine, Philadelphia, 1909; served during the World War; aged 56; formerly on the staff of the Ohio Soldiers' and Sailors' Orphans Home Hospital; on the staff of the McClellan Hospital, where he died, Nov. 27, 1940, of coronary thrombosis.

**Carey Andrew Gray** ☉ Bonham, Texas; Louisville (Ky.) Medical College, 1895; member of the House of Delegates of the American Medical Association in 1928; past president of the Fannin County Medical Society; on the staff of the S. B. Allen Memorial Hospital; aged 76; died, Oct. 13, 1940, of coronary thrombosis.

**Joseph Piedadue** ☉ Lewistown, Mont.; Victoria University Medical Department, Coburg, Ont., Canada, 1885; an Affiliate Fellow of the American Medical Association; for many years health officer of Bozeman and Gallatin County; aged 81; died, Nov. 27, 1940, in St. Vincent Hospital, Billings, of mitral stenosis.

**George Alfred Smith**, Clinton, Iowa; State University of Iowa College of Medicine, Iowa City, 1881; veteran of the Spanish-American War; formerly member of the state board of health; health officer; aged 86; died, Nov. 11, 1940, in the Jane Lamb Memorial Hospital of gastritis and colitis.

**George W. Poovey**, Lancaster, S. C.; College of Physicians and Surgeons, Baltimore, 1891; member of the South Carolina Medical Association; served during the World War; formerly mayor; aged 73; died, Nov. 2, 1940, of hypertension and angioneurotic edema of the tongue and pharynx.

**Solomon Seilikovitch**, Philadelphia; Medico-Chirurgical College of Philadelphia, 1893; member of the Medical Society of the State of Pennsylvania; formerly on the staff of the Mount Sinai Hospital; aged 75; died, Nov. 17, 1940, of hypertensive and arteriosclerotic cardiovascular disease.

**Frederick Merwin Heller** ☉ Pueblo, Colo.; Northwestern University Medical School, Chicago, 1912; on the staff of St. Mary Hospital; served during the World War; aged 56; died, Nov. 12, 1940, in Rochester, Minn., of edema of the lungs and coronary sclerosis.

**Thomas Alvin Hays** ☉ Burns City, Ind.; Medical College of Indiana, Indianapolis, 1892; an Affiliate Fellow of the American Medical Association; aged 78; died, Nov. 27, 1940, in the Daviess County Hospital, Washington, of valvular heart disease.

**Santiago Icasiano y Bello**, Bulacan, Philippine Islands; Universidad de Barcelona Facultad de Medicina, Spain, 1891; at one time chief physician of the Culion Leper Colony; aged 79; died, Sept. 6, 1940, in St. Anthony's Hospital of bronchopneumonia.

**Ellen Amelia Sherman**, McGregor, Iowa; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1879; member of the Iowa State Medical Society; aged 90; died, Nov. 2, 1940, of chronic myocarditis and senility.

**Reed Spencer Johnson**, Pikeville, Ky.; University of Louisville Medical Department, 1912; member of the Kentucky State Medical Association; on the staff of the Methodist Hospital; aged 58; died, Nov. 21, 1940, of carcinoma of the throat.

**Thomas Jefferson Patton**, Oxford, Ala.; Medical College of Alabama, Mobile, 1906; member of the Medical Association of the State of Alabama; aged 59; died, Nov. 3, 1940, at the Garner Hospital, Anniston, of acute duodenal ulcer.

**George Oates**, Grover, N. C.; University of Louisville (Ky.) Medical Department, 1894; member of the Medical Society of the State of North Carolina; aged 68; died, Nov. 2, 1940, in Rutherfordton of cerebral hemorrhage.

**Richard H. McCarty**, Saratoga Springs, N. Y.; Albany Medical College, 1886; member of the Medical Society of the State of New York; aged 75; died, Nov. 16, 1940, in the Saratoga Hospital of chronic glomerulonephritis.

**Beulah Marie Smith-Gruhn**, Chicago; University of Illinois College of Medicine, Chicago, 1925; aged 53; died, Oct. 6, 1940, in the Albert Merritt Billings Hospital of a cerebrovascular accident.

**Moses Emmett Morton**, Detroit; University of Michigan Medical School, Ann Arbor, 1918; member of the Michigan State Medical Society; aged 52; died, Nov. 12, 1940, of acute dilatation of the heart.

**John Charles Norton**, Baltimore; University of Maryland School of Medicine, Baltimore, 1912; served during the World War; police physician; aged 53; died, Nov. 10, 1940, of coronary thrombosis.

**Kenneth Lindsay Hood** ☉ Belvidere, Ill.; St. Louis University School of Medicine, 1926; president of the Boone County Medical Society; aged 45; died, Nov. 25, 1940, of acute nephritis.

**Helen Murphy**, Philadelphia; Woman's Medical College of Pennsylvania, Philadelphia, 1893; aged 80; died, Nov. 9, 1940, of carcinoma of the rectosigmoid and hypertensive cardiovascular renal disease.

**John Newton Beasley** ☉ Topeka, Kan.; St. Louis College of Physicians and Surgeons, 1897; on the staff of the Stormont Hospital; aged 66; died, Oct. 29, 1940, of carbon monoxide poisoning.

**Lester Irving Ofner**, Roads End, Calif.; University of Illinois College of Medicine, Chicago, 1915; aged 51; died, Nov. 27, 1940, in Santa Monica of streptococcus viridans infection.

**Roy La Fayette Owen**, Chicago; Rush Medical College, Chicago, 1901; aged 64; died, Nov. 25, 1940, in the Illinois Masonic Hospital of prostatic hypertrophy and pyelonephritis.

**Jesse Eugene Saunders**, Burket, Ind.; Curtis Physio-Medical Institute, Marion, 1895; aged 70; died, Nov. 10, 1940, in the McDonald Hospital, Warsaw, of carcinoma.

**Joe Newton Whittle**, Gladewater, Texas; St. Louis College of Physicians and Surgeons, 1901; aged 75; died, Oct. 25, 1940, of diabetes and cerebral hemorrhage.

**Frank J. Phipps**, Benton, Wis.; Milwaukee Medical College, 1896; aged 80; died, Nov. 7, 1940, in a hospital at Dubuque, Iowa, of arteriosclerosis.

**Cassius Adolphus Oliver**, Chico, Calif.; Pulte Medical College, Cincinnati, 1880; aged 84; died, Nov. 1, 1940, of coronary thrombosis.

**William Leonard Simmons**, Eastland, Texas; Baltimore Medical College, 1893; aged 70; died, Nov. 2, 1940, of cerebral hemorrhage.

**Montrose Day**, Haynesville, La.; Missouri Medical College, St. Louis, 1881; aged 85; died, Oct. 27, 1940, of coronary thrombosis.

## Correspondence

### THE NATURE OF THE SNELLEN VISUAL FORMULA

To the Editor:—In the remarks of Dr. Harry S. Grädle before the Annual Congress on Industrial Health (*THE JOURNAL*, March 16, p. 989) on the present status of estimating disability from visual loss, one is again reminded that the Snellen formula was never intended to be a fraction or ratio but is merely an expression of what appears to be a fraction.

In Webster's unabridged dictionary a fraction is defined as one or more aliquot parts of a unit or whole number, or an expression for a definite proportion of a unit or magnitude, and a ratio as the relation which one quantity or magnitude has to another of the same kind. In this connection, then, it is frequently contended that the Snellen formula could not be an aliquot part of unity, as represented by the norm 20/20, and therefore is not a true fraction. That this position is untenable has already been clearly set forth (Gabriels, J. A. C.: *The Snellen Symbol and Visual Value*, *Arch. Ophthalm.* 55:447 [Sept.] 1926); briefly, such visual notations as 20/30 and 20/40 have reference not to unity as indicated by 20/20 but to unity as expressed by 30/30 and 40/40, the subtending angle remaining the same as for the standard of 20/20, and each simply denoting one or more aliquot or equal parts of a linear unit. In like manner, there is in the Snellen formula a relation or comparison of two numerical values, namely 20/20 (20:20), or 20 to 20 feet, 20/30 (20:30), or 20 to 30 feet, 20/40 (20:40), or 20 to 40 feet, and so on. In the expression 20/20 the relation or ratio is 1 to 1, or unity; for 20/30, the ratio is 1 to 3, or two thirds; for 20/40, 2 to 4, or one half, and so on.

In this respect, too, witness the following: "The numerator represented the distance at which the chart should be read and the denominator the distance at which the chart actually was read. In other words, a vision of 20/20 means that the standard size chart, which should be read at 20 feet, was read at 20, whereas 20/40 means that at 20 feet the individual could only read that chart which should have been read at 40." What, may we ask, could more happily illustrate the meaning of a fraction, or ratio?

Further, it is stated that 20/50 is not 50 per cent loss of visual acuity. Obviously, by the simple process of *reductio ad absurdum*, this must be true—if the 10 minute visual angle represents a 50 per cent loss, then the 20 minute angle is a 100 per cent loss. Accordingly, the fractional unit cannot be the index of visual value. This is, however, hardly a valid argument against accepting these Snellen formulas as true fractions, as it has been shown that the actual or absolute measure of vision is based on the evaluation not of the fractional or linear unit but rather of the corresponding unit of surface area.

It should be pointed out that, to produce a visual impression, an object must subtend an angle of 1 minute or more, and this minimum visible applies equally to length and breadth—in short, is a two-dimensional perspective. This is the principle on which the Snellen test types are constructed. Hence all monocular vision is concerned not merely with the linear or one-dimensional unit but, in the final analysis, with the two-dimensional or surface area unit—a value which, in the estimation of visual loss on the Snellen basis, is equal to the ratio of the part to the whole in minute of angle square units (i. e., square of minutes of angle increase to square of minutes of whole angle), or in an equivalent sense the square of the unit of fractional loss. All this, indeed, becomes increasingly significant from a casual consideration of the physiologic phase of the visual act no less than from a study of the anatomic architecture of the retinal perceiving layer itself.

It must be plain, then, that the solution of this problem should follow along strictly objective lines, that it does not therefore lend itself to experimental methods, however ingenious, and that, as a matter of fact, this solution is as simple as the principle underlying the construction of Snellen characters themselves.

J. A. C. GABRIELS, M.D., Albany, N. Y.

### "APPLIED EPIDEMIOLOGY IN A GENERAL HOSPITAL"

To the Editor:—I have read with considerable interest the article by Dr. M. E. Barnes entitled "Applied Epidemiology in a General Hospital" in *THE JOURNAL*, Nov. 23, 1940, page 1757. Anticipating Dr. Barnes's ideas, the Bronx Hospital in New York has had an epidemiologist since December 1933. The pioneer work in this field was done at this institution and has proved a most valuable asset. For details concerning the general subject of the hospital epidemiologist I respectfully refer the reader to:

Felsen, Joseph: *The Prevention and Control of Outbreaks of Bacillary Dysentery*, *Bull. Am. Hosp. A.* 11:27 (March) 1937.

Felsen, Joseph: *Newer Concepts of Bacillary Dysentery and Other Types of Intestinal Infection*, *New York State J. Med.* 30:1582 (Aug. 15) 1939.

Felsen, Joseph, and Wolarsky, William: *The Hospital Epidemiologist*, *Hospitals* 14:41 (Aug.) 1940; reviewed in the *Year Book of Public Health*, J. C. Geiger, editor, Chicago, Year Book Publishers, Inc., 1940, p. 1.

The subject was also presented before the epidemiologic section of the American Public Health Association on Oct. 17, 1939, at which time the following seven point program for the prevention of infectious diarrheas was outlined:

1. International cooperation for detecting cases at their source.
2. Certification of passengers and crews of ships as to presence or absence of infectious diarrhea at points of embarkation and before disembarkation.
3. Compulsory universal reporting by physicians of all infectious diarrheas.
4. Adequate sanitary supervision of transportation systems, summer camps, food and food handlers.
5. Education of the physician and layman in isolating every case of diarrhea until cultures for specific organisms prove negative.
6. Appointment of an epidemiologist to the staff of every hospital.
7. The prophylactic use of vaccine and serum in bacillary dysentery.

While Dr. Felsen has concentrated chiefly on the prevention of bacillary dysentery and other infectious diarrheas, he has also repeatedly called attention to the value of the hospital epidemiologist in preventing other outbreaks frequently seen in hospitals.

LIONEL S. AUSTER, M.D., New York.

### "SURGICAL TREATMENT OF HYPERTENSION"

To the Editor:—In their article on the surgical treatment of hypertension (*THE JOURNAL*, Nov. 30, 1940, p. 1875) Peet, Woods and Braden state that bilateral supradiaphragmatic splanchnic nerve section and lower dorsal sympathetic ganglionectomy were first introduced into this country by Peet in 1933. Publications by Fenn and myself in the *Annals of Internal Medicine* (7:422 [Oct.] 1933 and 7:1201 [April] 1934) may easily have been overlooked by the authors. Later this operation was reported and illustrated in the *Annals of Surgery* (102:22 [July] 1935). Our first operation, as can be seen from the first publication, was done Oct. 22, 1932.

There is, of course, no question of priority in the matter, as Pieri adequately described and illustrated this approach in 1930 (*La cura chirurgica delle nevrosi gastriche*, Belluno, Tipografia Editrice "La Cartolibraria"). Since these early operations, which were done for juvenile diabetes, we have used the procedure for hypertensive patients but discontinued it in favor of Smithwick's method (*Surg.* 7:1 [Jan.] 1940).

GEZA DE TAKATS, M.D., Chicago.

## Medical Examinations and Licensure

### COMING EXAMINATIONS

#### BOARDS OF MEDICAL EXAMINERS BOARDS OF EXAMINERS IN THE BASIC SCIENCES

Examinations of boards of medical examiners and boards of examiners in the basic sciences were published in THE JOURNAL, January 4, page 71.

#### NATIONAL BOARD OF MEDICAL EXAMINERS

NATIONAL BOARD OF MEDICAL EXAMINERS: Parts I and II. Various centers, February 10-12. Exec. Sec., Mr. Everett S. Elwood, 225 S. 15th St., Philadelphia.

#### EXAMINING BOARDS IN SPECIALTIES

AMERICAN BOARD OF ANESTHESIOLOGY: *Oral*. Part II, Cleveland, May 31-June 1. Final date for filing application is April 1. Sec., Dr. Paul M. Wood, 745 Fifth Ave., New York.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY: Part II, Groups A and B, Cleveland, May 28-June 1. Final date for filing application is March 15. Sec., Dr. Paul Titus, 1015 Highland Bldg., Pittsburgh.

AMERICAN BOARD OF OPHTHALMOLOGY: *Oral*. Cleveland, May or June. Sec., Dr. John Green, 6830 Waterman Ave., St. Louis.

AMERICAN BOARD OF PATHOLOGY: *Oral and Written*. Cleveland, June 1-2. Final date for filing application is May 1. Sec., Dr. F. W. Hartman, Henry Ford Hospital, Detroit.

AMERICAN BOARD OF PEDIATRICS: Chicago, May 18, following the Region III meeting of the American Academy of Pediatrics. Boston, Oct. 12. Immediately following the annual meeting of the American Academy of Pediatrics. Sec., Dr. C. A. Aldrich, 723 Elm St., Winnetka, Ill.

AMERICAN BOARD OF RADIOLOGY. *Oral*. Cleveland, May 30-June 1. Final date for filing application is April 15. Sec., Dr. Byrl R. Kirklin, 102-110 Second Ave., S.W., Rochester, Minn.

AMERICAN BOARD OF SURGERY: *Written*. Part I. Various centers, April 2. Sec., Dr. J. Stewart Rodman, 225 South Fifteenth St., Philadelphia.

### California Reciprocity Report

Dr. Charles B. Pinkham, secretary, California State Board of Medical Examiners, reports 98 physicians licensed to practice medicine by reciprocity and 17 physicians so licensed by endorsement from May 9 through October 26. The following schools were represented:

School	LICENSED BY RECIPROCITY	Year Grad.	Reciprocity with
University of Arkansas School of Medicine.....	(1939)		Arkansas
University of California Medical School.....	(1934)		Missouri
George Washington University School of Medicine.....	(1935)		Dist. Colum.
Georgetown University School of Medicine.....	(1929)		Michigan
Howard Univ. College of Medicine (1929) New York, (1932)			Kansas
American Medical Missionary College.....	(1909)		Michigan
Loyola University School of Medicine.....	(1929)		Illinois
Northwestern University Medical School.....	(1936)		Illinois
Rush Medical College.....	(1917), (1930)		Wisconsin,
(1932) Colorado, (1937) Michigan			
Univ. of Illinois College of Medicine (1914), (1930), (1934)			Illinois,
(1925) South Dakota, (1930) Arizona			
Indiana University School of Medicine.....	(1932), (1936)		Indiana
State Univ. of Iowa College of Medicine (1911), (1916), (1936)			Iowa
University of Kansas School of Medicine..(1933), (1938, 2)			Kansas,
(1936) Minnesota			
University of Louisville School of Medicine.....	(1936)		Kentucky
Johns Hopkins University School of Medicine.....	(1916)		Dist. Colum.
University of Maryland School of Medicine and College			
of Physicians and Surgeons.....	(1937)		Maryland
Boston University School of Medicine.....	(1932)		Mass.
Harvard Medical School.....	(1915), (1935)		Minnesota
Univ. of Michigan Dept. of Medicine and Surgery.....	(1912)		Michigan
University of Michigan Medical School.....	(1920), (1932)		Michigan
Univ. of Minnesota Medical S.....	(1938)		Minnesota
St. Louis University School.....	(1939)		Missouri
Creighton Univ. School of Medicine..(1926), (1928), (1931)			Nebraska
John A. Creighton Medical College.....	(1917)		Nebraska
University of Nebraska College of Medicine..(1932), (1935)			Washington,
(1932), (1934, 2), (1935), (1939) Nebraska			
Columbia Univ. College of Physicians and Surgeons (1925),			
(1930), (1931), (1935, 2) New York			
Cornell University Medical College.....	(1937)		Penna.
Long Island College Hospital.....	(1909)		New York
Syracuse University College of Medicine.....	(1927)		New York
University of Rochester School of Medicine and Den-			
tistry.....	(1921), (1931), (1932)		New York
Ohio State University.....			Ohio
University of Cincinnati.....			Ohio
Western Reserve Univ.....			New York
University of Oklahoma School of Medicine.....	(1936)		Oklahoma
University of Oregon Medical School (1930), (1935), (1936),			
(1938) Oregon			
Hahnemann Med. College and Hospital of Philadelphia (1935)			Maine
Jefferson Medical College of Penna.....			Penna.
Medico-Chirurgical College of Penna.....			Penna.
Temple University School of Penna.....			Penna.
University of Pennsylvania Sch.....			Minnesota,
(1936), (1937) Pennsylvania, (1936) New York			
University of Tennessee College of Medicine (1930), (1937, 2)			Tennessee,
(1938) Mississippi			
University of Texas Faculty of Medicine.....	(1937)		Texas
University of Virginia Department of Medicine.....(1933)			Virginia,
(1934) Minnesota			
Marquette University School of Medicine....(1928), (1933)			Wisconsin
University of Wisconsin Medical School.....(1933)			Wisconsin

University of Alberta Faculty of Medicine.....	(1925)	Michigan
University of Toronto Faculty of Medicine.....	(1916)	Colorado,
(1925) Illinois		
McGill University Faculty of Medicine.....	(1935)	Washington
Albertus-Universität Medizinische Fakultät, Königsburg.....	(1927)	Illinois
University of St. Andrews Conjoint Medical School....	(1934)	New York

School	LICENSED BY ENDORSEMENT	Year Grad.	Endorsement of
College of Medical Evangelists.....	(1935, 2), (1937)	(1939)	N. B. M. Ex.
University of Colorado School of Medicine.....	(1934)		N. B. M. Ex.
George Washington University School of Medicine....	(1934)		N. B. M. Ex.
Northwestern University Medical School.....	(1937)		N. B. M. Ex.
Rush Medical College.....	(1926), (1937)		N. B. M. Ex.
University of Illinois College of Medicine.....	(1932)		N. B. M. Ex.
Harvard Medical School.....	(1933)		N. B. M. Ex.
University of Minnesota Medical School.....	(1938)		N. B. M. Ex.
Columbia University College of Physicians and Sur-			
geons.....	(1932)		N. B. M. Ex.
Cornell University Medical College.....	(1933)		N. B. M. Ex.
New York Medical College and Flower Hospital.....	(1937)		N. B. M. Ex.
Duke University School of Medicine.....	(1937)		N. B. M. Ex.
University of Pennsylvania School of Medicine.....	(1933)		N. B. M. Ex.

### Maine July Report

Dr. Adam P. Leighton, secretary, Board of Registration of Medicine, reports the written examination for medical licensure held at Augusta, July 2-3, 1940. The examination covered 10 subjects and included 100 questions. An average of 75 per cent was required to pass. Fifteen candidates were examined, 10 of whom passed and 5 failed. Two physicians were licensed to practice medicine by reciprocity and 3 physicians so licensed by endorsement. The following schools were represented:

School	PASSED	Year Grad.	Per Cent
Georgetown University School of Medicine.....	(1938)		86
Tufts College Medical School.....	(1913) 80, (1940)		81
Univ. of Rochester School of Medicine and Dentistry	(1939)		77
University of Pennsylvania School of Medicine.....	(1940)	86,	87
Queens University Faculty of Medicine.....	(1933)		81
McGill University Faculty of Medicine.....	(1940)		88
Regia Università degli Studi Roma. Facoltà di Medi-			
cina e Chirurgia.....	(1937)		77
Universität Bern Medizinische Fakultät.....	(1936)		79

School	FAILED	Year Grad.	Number Failed
Boston University School of Medicine.....	(1933)		1
Columbia Univ. College of Physicians and Surgeons	(1937)		1
University of Montreal Faculty of Medicine.....	(1940)		1
Regia Università degli Studi Bologna. Facoltà di			
Medicina e Chirurgia.....	(1937)		1
Universität Bern Medizinische Fakultät.....	(1938)		1

School	LICENSED BY RECIPROCITY	Year Grad.	Reciprocity with
Yale University School of Medicine.....	(1920)		New Hamp.
Jefferson Medical College of Philadelphia.....	(1936)		Penna.

School	LICENSED BY ENDORSEMENT	Year Grad.	Endorsement of
Harvard Medical School.....	(1938)		N. B. M. Ex.
New York Medical College and Flower Hospital.....	(1937)		N. B. M. Ex.
Duke University School of Medicine.....	(1936)		N. B. M. Ex.

## Bureau of Legal Medicine and Legislation

### MEDICOLEGAL ABSTRACTS

**Medical Practice Act (New York): Alleged Arbitrary Refusal of Board of Regents to Indorse Foreign Licenses.**—Emerson Stanley Bailey, the petitioner, graduated from Leonard Medical College in 1905. Later that year after examination he was licensed to practice medicine and surgery in Massachusetts. He was likewise licensed in New Jersey in 1905; in West Virginia, 1909; in the District of Columbia, 1910; in Missouri, 1911, and in Ohio, 1923. Since 1905 he had been actively engaged in the practice of medicine and surgery. He served as an intern in Freedman's Hospital in Washington, D. C., from 1908 to 1910. He then became executive superintendent of Provident Hospital, St. Louis, but just how long he so served is not stated. From 1915 to 1918 he owned and operated "The Bailey Sanitarium" in St. Louis, which was licensed and supervised by the State of Missouri. From 1918 to 1928 and from 1932 to date he served as visiting surgeon at People's Hospital, St. Louis; from 1933 to date,

as chief orthopedist at St. Mary's Infirmary, St. Louis, and from 1920 to 1929, as associate visiting surgeon at the Homer G. Phillip's Hospital, St. Louis, and thereafter as visiting surgeon and a member of the dispensary staff at that institution. He is a member in good standing of the Medical Society of the City of St. Louis, of the State of Missouri Medical Society and of the National Medical Association.

On several occasions Bailey sought to be examined for a license to practice medicine and surgery in New York but he was denied the right to be examined on the ground that the medical school from which he graduated was not registered with the Department of Education of the State of New York and that it would be necessary for him to study two additional years in a registered medical school and obtain a degree therefrom before he could be examined. In 1939 he applied to the Board of Regents of the University of the State of New York requesting it to indorse the licenses he had received to practice in Massachusetts, New Jersey, the District of Columbia, Missouri, West Virginia and Ohio, which action, in effect, would permit him to practice in New York. The board denied his application without assigning any written reasons for its action and Bailey brought mandamus proceedings in the supreme court, special term, Albany County, N. Y., to compel the board to indorse the licenses referred to, alleging that the board in denying his application had acted unfairly, arbitrarily and capriciously.

Section 51 of the New York Education Law authorizes the Board of Regents to indorse a license issued by a legally constituted board of examiners in any other state or country on satisfactory evidence that the requirements for the issuance of such license were substantially the equivalent of the requirements in force in New York when such license was issued if the applicant has been in lawful and reputable practice of his profession for not less than five years prior to his application. The State of New York contended that under this statute an application for indorsement is addressed to the board's discretion and mandamus will not lie to compel the board to exercise its discretion in the petitioner's behalf. The discretion of the board, said the supreme court, while broad and rightly so, is not an absolute finality. It is conclusive when and only when it accords with the law as to what ought to have been done in the particular proceeding. Since the decision of the board conclusively determines the substantial rights of the petitioner, it is the duty of this court on an allegation that the board's action was unfair, arbitrary and capricious to inquire into the facts, and if on a fair consideration of all the circumstances and the law it was the duty of the board to grant the petitioner the relief he sought, this court must reverse the improper action and correct the wrong done. Discretion when exercised must be a sound judicial discretion and not an arbitrary act or whim.

New York, Ohio and New Jersey, continued the court, have entered into "reciprocity medical agreements" as to the issuance of licenses to practice medicine which provide that "Full faith and credit shall be given by the (licensing) board of each state to the medical examinations held by the board of either state." The record shows that the petitioner was licensed to practice medicine in Ohio in 1923. If New York State will indorse without examination an individual admitted to practice medicine in Ohio, it cannot be justly said as a matter of law that the minimum required standards of education, training and experience are lower in Ohio than in New York. It is true that in reciprocity agreements New York reserves the right to examine into the preliminary and professional education of the applicants, but like all agreements such a provision is not to be narrowly construed. Its interpretation must comport with reason and common sense, and in support of the entire instrument and its purpose. Each reciprocity agreement demands that the applicant for indorsement must first show that he is a reputable practitioner of medicine in good standing in his community and in his profession. Candidates licensed on examination under lower requirements than those now existing

in the states may submit evidence of five years of reputable practice subsequent to the earning of their medical degree, which may be accepted in lieu of the preliminary and the first year of the professional requirements for the indorsement of their licenses.

The court then adverted to the fact that section 1257 of the Education Law requires applicants for licenses on the basis of examination to be examined in anatomy, physiology, hygiene, chemistry, surgery, obstetrics, gynecology, pathology, bacteriology and diagnosis. The court pointed out that the petitioner had been examined in all the statutory required subjects just stated either in New Jersey or in Massachusetts, or in both states, and that he had attained an average mark of 80 per cent in the examinations. The court also remarked that at the medical school which he attended the petitioner was taught by professors who were also professors on the faculty of the Medical School of the University of North Carolina, men who were generally recognized as possessing high qualifications and excellent reputations.

After a man has actively practiced medicine for twenty-five years and has been duly licensed to practice in five states, it is foolish, ridiculous and silly, said the court, to require him to go back to a medical school and study two years more to earn another degree, and then present himself for examination to be admitted in another state. Such a demand seems to us one in defiance of all reason. The court then adverted to section 1259 of the Education Law, which authorized the commissioner of education in his discretion, on the approval of the Board of Regents, to indorse a license or diploma of a physician from another state, or country, if the applicant has met all the preliminary and professional qualifications required for earning a license on examination in this state, has been in reputable practice for a period of ten years and has reached a position of conceded eminence and authority in his profession. No one, continued the court, can reasonably question the fact that the record shows that the petitioner has been more than the usual ordinary practitioner of medicine. It may be that on close analysis he does not come within the definition medically of a doctor who is eminent and an authority in his profession, but at least he is very well known and of more than ordinary ability.

While the supreme court did not grant the petition for a writ of mandamus, it believed that on the whole record there was no reasonable basis for apprehension regarding the petitioner's medical fitness. Accordingly, the court directed that the action of the Board of Regents in refusing the petitioner's application should be reviewed by the appellate division of the supreme court of New York, third judicial department, and so it transferred the proceedings thereto.—*Application of Bailey, 20 N. Y. S. (2d) 915 (N. Y., 1940).*

## Society Proceedings

### COMING MEETINGS

- Annual Congress on Industrial Health, Chicago, Jan. 13-15. Dr. Carl M. Peterson, 535 N. Dearborn St., Chicago, Secretary.
- Annual Congress on Medical Education and Licensure, Chicago, Feb. 17-18. Dr. W. D. Cutter, 535 North Dearborn St., Chicago, Secretary.
- American Orthopsychiatric Association, New York, Feb. 20-22. Dr. Norville C. La Mar, 149 East 73d Street, New York, Secretary.
- Central Surgical Association, Ann Arbor, Mich., Feb. 28-March 1. Dr. George M. Curtis, Ohio State University, Columbus, Ohio, Secretary.
- Middle Section, American Laryngological, Rhinological and Otolological Society, Chicago, Jan. 27. Dr. Walter H. Theobald, 307 North Michigan Blvd., Chicago, Chairman.
- Pacific Coast Surgical Association, Los Angeles, Feb. 19-22. Dr. H. Glenn Bell, University of California Hospital, San Francisco, Secretary.
- Society of Surgeons of New Jersey, Newark, Jan. 29. Dr. Walter B. Mount, 21 Plymouth St., Montclair, Secretary.
- Society of University Surgeons, St. Louis, Feb. 14-15. Dr. Frank Glenn, 525 East 68th St., New York, Secretary.
- Western Section, American Laryngological, Rhinological and Otolological Society, San Francisco, Feb. 1-2. Dr. Robert C. Martin, 384 Post St., San Francisco, Chairman.

## Current Medical Literature

### AMERICAN

The Association library lends periodicals to members of the Association and to individual subscribers in continental United States and Canada for a period of three days. Three journals may be borrowed at a time. Periodicals are available from 1930 to date. Requests for issues of earlier date cannot be filled. Requests should be accompanied by stamps to cover postage (6 cents if one and 18 cents if three periodicals are requested). Periodicals published by the American Medical Association are not available for lending but can be supplied on purchase order. Reprints as a rule are the property of authors and can be obtained for permanent possession only from them.

Titles marked with an asterisk (\*) are abstracted below.

### American Heart Journal, St. Louis

20:519-654 (Nov.) 1940

- Effect of Distention of Abdominal Viscera on Blood Flow in Circumflex Branch of Left Coronary Artery of Dog. N. C. Gilbert, G. V. LeRoy and G. K. Fenn, Chicago.—p. 519.
- Effect of Transplanted Ischemic Kidneys and of Temporary, Complete, Renal Ischemia on Blood Pressure of Rabbits. M. Prinzmetal, H. A. Lewis, J. Taggart, H. Wilkins and D. R. Drury, Los Angeles.—p. 525.
- Role of Arteriovenous Anastomosis in Peripheral Vascular Disease. K. Harpuder, I. D. Stein and J. Byer, New York.—p. 539.
- Cardiac Hypertrophy Caused by Glycogen Storage Disease in a Fifteen Year Old Boy. W. Antopol, E. P. Boas, W. Levison and L. R. Tuchman, New York.—p. 546.
- Simultaneous Action of Certain Drugs on Blood Pressure and on Flow in Right and Left Coronary Arteries. R. Wégria, H. E. Essex, J. F. Herrick and F. C. Mann, Rochester, Minn.—p. 557.
- Studies on Auriculoventricular Conduction Time of Normal Children and of Rheumatic Children Without Signs of Rheumatic Activity. Gertrude Meyersbach and Ann G. Kuttner, Irvington-on-Hudson, N. Y.—p. 573.
- Influence of Digitalis on Electrolyte and Water Balance of Heart Muscle. P. K. Boyer and C. A. Poindexter, New York.—p. 586.
- Significance of Position of Subject in Evaluation of Electrocardiogram. L. S. Ylvisaker and H. B. Kirkland, Newark, N. J.—p. 592.
- Chromatrophic Degeneration and Rupture of Aorta Following Thyroidectomy in Cases of Hypertension. W. B. Kountz and L. H. Hempelmann, St. Louis.—p. 599.
- Observations on Cardiovascular System in Myasthenia Gravis. A. C. Taquini, W. T. Cooke and R. S. Schwab, Boston.—p. 611.
- \*Effect of Intravenous Administration of Quinidine Sulfate on Development of Ventricular Fibrillation Following Sudden Occlusion of Circumflex Branch of Left Coronary Artery: Experimental Study. F. H. Smith, C. G. McEachern and G. E. Hall, Toronto.—p. 620.
- Left Auricle with Capacity of 1,695 Gm. of Blood in Case of Mitral Stenosis. R. L. Nelson, Duluth, Minn.—p. 627.
- \*Long Survival Following Coronary Thrombosis. E. H. Drake, Portland, Maine.—p. 634.
- \*Terminal Cardiac Mechanism in Coronary Artery Disease: Report of Two Cases. B. E. Goodrich, Detroit, and R. J. Needles, St. Petersburg, Fla.—p. 637.

**Quinidine Sulfate and Ventricular Fibrillation.**—Smith and his associates observed the effect of intravenous quinidine sulfate on the development of ventricular tachycardia and ventricular fibrillation produced by ligating the coronary artery in conscious dogs. The quinidine sulfate definitely accelerated the heart rate of all animals. In a few instances isolated extrasystoles were also observed. Within two or three seconds of ligation many extrasystoles appeared, and within ten seconds the normal ventricular complexes were replaced by long runs of ventricular extrasystoles. Ventricular tachycardia became well established almost immediately. In the animals that eventually recovered after ventricular tachycardia was maintained for some time, the ventricular complexes became irregular in shape, rate and amplitude. A progressive decrease in the amplitude of the ventricular complex, together with better definition of the RT segment, followed and the beating became progressively more regular until after about thirty minutes the auricular and ventricular complexes approximated the normal. Axis deviation developed within the next few days. Within eighteen to twenty-four days the electrocardiogram was essentially normal. Likewise the electrocardiograms of the dogs which died showed a rapid elevation of the RT segment, a high take-off of the T wave, a marked increase in the amplitude of the waves and an early absence of P waves. The early ventricular tachycardia was soon followed by true ventricular fibrillation. Fatal ventricular fibrillation almost always developed within ninety seconds of ligation. The doses of quinidine sulfate were relatively large but not grossly out of proportion to those used clinically. Quinidine sulfate does abolish almost completely cardiac pain, suggesting that pain pathways are separate from those which produce fibrillation

reflexly. It renders the dog's myocardium more susceptible to the development of cardiac irregularities. Extrasystoles of left and right ventricular origin were recorded. Quinidine sulfate lowers the mortality of coronary occlusion in dogs. The mortality among 20 animals was 55 per cent as compared to 75 per cent in a control series.

**Long Survival Following Coronary Thrombosis.**—Drake reports the survival of a man (a telegrapher) for nearly forty years after coronary thrombosis. He was first seen by Drake at the age of 72, seven years before death, when he had suffered from angina for five years. The patient stated that he had experienced the same pain at the age of 40, except that at this time the pain was more severe and that it had gradually increased in intensity, came at more frequent intervals and was more easily precipitated. This state continued for several weeks, but since then the pain had not returned for twenty-seven years. At an examination in 1933 hypertension and cardiac enlargement were present. In 1935 the patient suffered a coronary thrombosis from which recovery was uneventful except for a complicating attack of arthritis. Following this he continued to have infrequent attacks of mild angina pectoris easily relieved by glyceryl trinitrate. At the age of 77 he retired. In 1938 another coronary thrombosis occurred. This attack was severe, was accompanied by marked pulmonary edema and was followed by frequent severe recurrences of pain and by cerebral embolism and left hemiplegia. He was confined to bed for four months. Infrequent attacks of angina pectoris continued. Prostatic hypertrophy, which caused nocturia, developed and unless he voided promptly on awakening an attack of angina pectoris would result. Because he feared the cardiac pain he occasionally took glyceryl trinitrate at these times to forestall an attack. On Oct. 2, 1939 he awakened with a desire to void and experienced an attack of angina pectoris which was not relieved by glyceryl trinitrate. A hypodermic injection of morphine was ordered; a half hour later he was unconscious and died within a few minutes. The body was embalmed before permission for necropsy was obtained and therefore the heart was considered unsuitable for injection studies. The heart weighed only 360 Gm. Old obstructions, with calcification, were found in the left anterior descending branch, a large branch of the left circumflex and the right circumflex artery. There were three fair-sized areas of fibrosis in the ventricular walls; the most recent one was in the posterior basal portion of the left ventricle. There was no fresh coronary thrombosis to explain the fatal attack. It seems certain that one of the three scars resulted from the myocardial infarction suffered at the age of 40. It seems that certain middle-aged patients may recover completely from coronary thrombosis and live out their span of life.

**Terminal Cardiac Mechanism in Coronary Artery Disease.**—Goodrich and Needles cite 2 instances in which they observed on electrocardiographic study the terminal cardiac mechanism of sudden death from coronary artery disease. One of the deaths was shown at necropsy to have been caused by marked coronary artery sclerosis (the patient had had angina pectoris). The other was the result of infarction of the anterior wall of the heart; it occurred on the tenth day after coronary occlusion. The first case supports the contention of Grieco and Schwartz that cardiac standstill should occur as frequently as ventricular fibrillation, and that if more records could be obtained additional instances of cardiac standstill would probably be discovered.

### American Journal of Clinical Pathology, Baltimore

10:771-852 (Nov.) 1940

- Evolution of Biologic Pathology from Ancient Animistic Beliefs. B. L. Gordon, Atlantic City, N. J.—p. 771.
- Normal Nonfilament-Filament Count and Its Relation to Schilling Count. M. H. Stiles, E. F. Dirickx and M. T. Stiles, Philadelphia.—p. 783.
- Aplastic Anemia. L. E. January and W. M. Fowler, Iowa City.—p. 792.
- Hypertension and Kidney Function: Relationship of Albuminuria to Blood Pressure, Weight, Body Build and Surface Area. M. Brucer and S. C. Robinson, Chicago.—p. 800.
- Possible Factors in Reaction of Tumors to Local Asphyxia. F. M. Allen, New York.—p. 813.
- Virilism Associated with Adrenal Cell Rest Tumor. S. S. Zuckerman, Cheyenne, Wyo., and H. E. Stuckenhoff, Casper, Wyo.—p. 822.

## American J. Digestive Diseases, Huntington, Ind.

7:447-512 (Nov.) 1940

- Congenital Diaphragmatic Hernia: Report of Successfully Operated Case. J. H. Willard, Philadelphia.—p. 447.
- I. Experimental Study of Effect of Pituitary on Motility of Gastrointestinal Tract: Preliminary Report. S. Morrison and M. Feldman, Baltimore.—p. 451.
- II. Experimental Study of Effects of Pituitary and Thyroid Glands on Carbohydrate Metabolism: Preliminary Report. S. Morrison and M. Feldman, Baltimore.—p. 453.
- Fate of Ingested Glucose Solutions of Various Concentrations at Different Levels of Small Intestine. H. Shay, J. Gershon-Cohen, S. S. Fels and F. L. Munro, Philadelphia.—p. 456.
- Factors Influencing Digestion in Jejunum. L. C. McGee and E. S. Emery Jr., Boston.—p. 462.
- Intubation Studies of Human Small Intestine: XX. Diagnostic Significance of Motor Disturbances. F. J. Ingelfinger and W. O. Abbott, Philadelphia.—p. 468.
- Roenigkologic Diagnosis of Diseases of Small Intestine. B. R. Kirklin and H. M. Weber, Rochester, Minn.—p. 475.
- Changes in Small Intestine Associated with Deficiency Disease. T. T. Mackie and M. A. Mills, New York.—p. 480.
- \*Further Observations on Clinical Use of Vitamin K. J. F. Weir, H. R. Butt and A. M. Snell, Rochester, Minn.—p. 485.
- Blood in Cases of Hematemesis and Melena with Reference to Factors Influencing Hemorrhage. H. K. Moss, L. Schiff, R. L. Stevens and M. L. Rich, with technical assistance of Ellen S. Garber, Cincinnati.—p. 490.
- Present Status of Gastrectomy. I. Abell, Louisville, Ky.—p. 495.
- Gastrectomy, Partial, Subtotal and Total, Radiographic Phase. W. H. Stewart, New York.—p. 498.
- Effects of Gastrectomy in Animals. A. C. Ivy, Chicago.—p. 500.
- \*Problem of Gastrectomy and Anemias. C. M. Jones, Boston.—p. 502.
- Gastroscopic Observations in Resected Stomachs. R. Schindler, Chicago.—p. 505.

**Clinical Use of Vitamin K.**—According to Weir and his associates, the danger of postoperative hypoprothrombinemia in severe degrees of cholecystic and biliary infection has not been generally appreciated. Hypoprothrombinemia and hemorrhagic diathesis have been demonstrated in intestinal polyposis, regional ileitis, intestinal obstruction, gastrocolic fistula, pyloric obstruction and ulcerative colitis. Under such conditions a deficient diet, loss of essential substances by vomiting and diarrhea and an abnormal mucosal surface of the gastrointestinal canal are sufficient to deplete prothrombin. As in jaundice the deficiency does not become serious until after some surgical procedure designed to correct the primary condition has been performed. Whatever the mechanism causing vitamin K deficiency in biliary obstruction or infection, the prothrombin coagulation time has solved the mystery of obscure intestinal bleeding previously responsible for much postoperative morbidity and mortality. Since the availability of synthetic compounds of vitamin K the authors have used four with excellent results. Phthiocol was administered in doses of 25 to 50 mg. intravenously to 9 of 10 patients. The delayed prothrombin time was corrected, and bleeding in one case was controlled. The "naphthaldehyde" compound 1,4-dihydroxy-2-methyl-3-naphthaldehyde was given intravenously to 10 patients in doses of 10 to 20 mg. with satisfactory results except in 2 cases of cirrhosis. The preparation 2-methyl-1, 4-naphthoquinone was administered orally to 20 patients in tablets of 1, 2, 3 and 5 mg. In most instances the elevated prothrombin clotting time returned to normal within thirty-six hours after its administration. In other cases a soluble salt of this compound, 2-methyl-1, 4-naphthohydroquinone-sodium sulfonate, was given intravenously in doses equivalent to 2 mg. of 2-methyl-1, 4-naphthoquinone. Its action was prompt and effective. No untoward reactions occurred. The results were not satisfactory in 3 cases in which there was some form of cirrhosis of the liver with marked impairment of hepatic function. The authors have tried a soluble compound, vitamin K<sub>2</sub> (4-amino-2-methylnaphthol hydrochloride) suitable for intravenous administration. It was given to 26 patients with jaundice and 13 with gastrointestinal and miscellaneous lesions. In 6 cases of obstructive jaundice with a prolonged prothrombin clotting time this defect was readily controlled. Bleeding was encountered in 1 case and was controlled. In 1 case of severe disease of the gallbladder with hepatitis but without biliary obstruction a delayed prothrombin clotting time developed several days postoperatively and was readily controlled. In 4 cases of intestinal disease with delayed prothrombin clotting time but without bleeding, similar good results were obtained. Failure was encountered in 3 cases of cirrhosis. In 1 other case evidence of bleeding was satisfactorily controlled. The treatment in the remaining cases was prophylactic and no manifestations of bleeding were encountered

at any time during the period of illness. The action of these compounds is extremely rapid and suggests a possible enzymatic activity.

**Gastrectomy and Anemia.**—Jones points out that animal experimentation, although of extreme interest to the development of an iron deficiency anemia after subtotal or total gastrectomy, has not indicated the exact source of the antianemic factor demonstrated by Castle to be present in human gastric juice. It is still impossible to translate to man, except by analogy, the results obtained after gastric resection in animals. In all animal experiments, anemia following gastric resection developed only after months or years except in the presence of other factors, such as pregnancy. Two micropathologic studies suggest that in man also the macrocytic anemia characteristic of Addisonian anemia does not develop unless important extra-gastric lesions coexist in the digestive tract. Brown showed what he interpreted as widespread evidence of enteritis in a large number of necropsy specimens from patients dying of pernicious anemia. However, because of failure to fix the tissues immediately after death these studies are open to question. Of much greater suggestive interest is the microscopic study by Jacobson of material from the stomach and intestines from various animals and human beings dying of pernicious anemia, sprue and certain other diseases. Jacobson points out the striking parallelism in the distribution of argentaffine cells in man and in the pig and the localization of the principle active against pernicious anemia in the mucosa of the gastrointestinal tract. In patients dying of pernicious anemia the argentaffine cells are completely or almost completely absent. He suggests that these particular cells are responsible for the secretion of Castle's intrinsic factor but admits that convincing proof is lacking. In spite of complete proof, on the basis of animal experimentation, a primary Addisonian anemia in man as a sequel to partial or total gastrectomy is rarely to be expected. Clinical reports are fully in accord with such an assumption. Therefore it is apparent that major gastric surgery—subtotal or total gastrectomy—may be performed without fear of undue consequences to normal hemopoiesis. In spite of the relative or absolute achlorhydria that results and that secretory cells of importance to normal blood physiology may be removed, serious anemias need not be feared. An occasional severe microcytic or macrocytic anemia may in time ensue. However, in all probability such anemias are readily treated with iron or liver. The search for the site at which the intrinsic antianemic factor is formed must be pursued, but lack of accurate knowledge as to its source need not preclude proper gastric surgery.

## American Journal of Hygiene, Baltimore

32:67-92 Section A (Nov.) 1940. Partial Index

55-80 Section B 63-112 Section C 85-132 Section D

## Section A

- Tuberculosis in Married Couples. J. F. Paterson, Philadelphia.—p. 67.
- Relationship of Immediate Family Contact to Transmission of Type Specific Pneumococci. W. G. Smillie and Olga F. Jewett, New York.—p. 79.
- Secondary Familial Attack Rates from Pertussis in Vaccinated and Unvaccinated Children. Pearl L. Kendrick, Grand Rapids, Mich.—p. 89.

## Section B

- Canine Rabies Vaccination: Experimental Study of Efficacy of Single Intraperitoneal Injection Method with Phenol-Treated Vaccine. H. N. Johnson and C. N. Leach, Montgomery, Ala.—p. 69.
- Id.: Experimental Study of Efficacy of Single Subcutaneous Injection Method with Chloroform-Treated Vaccine. C. N. Leach and H. N. Johnson, Montgomery, Ala.—p. 74.

## Section C

- Studies on Induced Quartan Malaria in Negro Paretics: II. Effect of Modifying the External Conditions. M. D. Young, G. R. Coatsy and T. H. Stubbs, Columbia, S. C.—p. 63.
- Supernucleate Cysts of Endamoeba Coli. M. M. Brooke, Mexico, D. F., Mexico.—p. 100.

## Section D

- Studies on Schistosome Dermatitis: VIII. Notes on Biology of Snail Hosts of Schistosome Cercariae in Wisconsin and Epidemiologic Evidence for Life Cycles of Some Avian Schistosomes. S. Brackett, Madison, Wis.—p. 85.
- Rapid Loss of Trichinella Larvae Fed to Immune Rats and Its Bearing on Mechanism of Immunity. O. R. McCoy, Rochester, N. Y.—p. 105.
- Relative Effectiveness of Iron and Anthelmintics in Treatment of Hookworm Anemia. G. C. Payne and Florence King Payne, Mexico, D. F., Mexico.—p. 125.



## American J. Obstetrics and Gynecology, St. Louis

40:727-924 (Nov.) 1940

- Comparative Anatomy and Pharmacology of Pituitary Gland of Unusual "Experimental" Animals. E. M. K. Geiling, Chicago.—p. 727.
- \*Functional and Growth Characteristics of Struma Ovarii. L. A. Emge, San Francisco.—p. 738.
- \*Carcinoma of Ovary. F. A. Pemberton, Boston.—p. 751.
- \*Cancer of Vulva: Analysis of 155 Cases (1911-1940). F. J. Taussig, St. Louis.—p. 764.
- Carcinoma of Cervix After Supravaginal Hysterectomy. C. A. Behney, Philadelphia.—p. 780.
- Carcinoma of Body of Uterus. N. F. Miller, Ann Arbor, Mich.—p. 791.
- Primary Cancer of Fallopian Tube: Consideration of Its Incidence, Clinical Diagnosis and Treatment, with Report of Case Diagnosed Before Operation. K. H. Martzloff, Portland, Ore.—p. 804.
- Fibromyoma of Uterus. G. H. Gardner, Chicago.—p. 822.
- Endometriosis: A Review of the Literature and Clinical Study. J. E. Hobbs and A. R. —p. 832.
- Vitamin K in Obstetrics: Review of One Year's Experience. L. M. Hellman, L. B. Shettles and N. J. Eastman, Baltimore.—p. 844.
- Management of Adherent Placenta in Presence of Infection. K. M. Wilson, Rochester, N. Y.—p. 854.
- Comparison of Two Cesarean Section Surveys Carried on in the City of New Orleans. E. L. King, New Orleans.—p. 860.
- Pseudohermaphroditism. J. P. Pratt, Detroit.—p. 870.
- Pathogenicity and Physiology of Pure Culture of *Trichomonas Vaginalis*. R. E. Trussell and E. D. Plass, Iowa City.—p. 883.
- Roentgen Pelvimetry as Routine Prenatal Procedure. H. Thoms, New Haven, Conn.—p. 891.
- Simple Method of Making an Artificial Vagina. F. H. Falls, Chicago.—p. 906.

**Functional and Growth Characteristics of Ovarian Struma.**—According to Emge, casual statistics place ovarian strumas between 2 and 15 per cent of ovarian teratomas, usually dermoids. In his material the incidence was 4 per cent. An ovarian struma (and not necessarily a large one), under conditions yet unexplained, can seriously unbalance the metabolism of the body and at times invade other tissues through metastatic growth. Eight strumas of the ovary that have produced metastases, and a slightly larger number described as having caused thyrotoxic symptoms, have been reported. The author has encountered 2 instances of hyperthyroidism accompanying such tumors, 1 of which also produced extensive metastases. Most ovarian strumas are silent and are usually discovered accidentally at routine pelvic examinations or operation. The tumor in 1 of the author's patients was active enough functionally to disturb metabolism. The hyperthyroidism was corrected by removal of the ovarian struma. Most ovarian strumas are benign tumors with orderly growth habits. They are more common after maturity and to the author's knowledge have not been encountered in childhood. When part of an ordinary teratoma, they may freely intermingle with other tissue. When pure struma, they have a capsule formed by mesoderm derivatives. The morphologic structure of the tumor does not necessarily indicate its functional activity. Large tumors do not always present a uniform morphologic picture but may show various stages of cellular activity in different areas of the tumor. Generally their tendency is to develop into a colloid goiter rather than to maintain hyperplastic activities. When the latter is present, different degrees of hyperplastic action may occur within the same tumor. The severer types of hyperplasia are rarely encountered. From 5 to 6 per cent of these tumors may be expected to assume metastatic habits, which is not necessarily fatal. Metastases from an ovarian thyroid are usually superficial and ordinarily confined to the abdominal viscera. The presence of metastases may or may not disturb the patient's health. The author's patient, though still harboring a large amount of aberrant tissue, is in good health. Two surveys (a year apart) have failed to demonstrate osseous metastatic invasion, indicating the relatively benign character of the growth. Patients may live many years with multiple aberrant thyroids. Whether irradiation can arrest the growth of metastatic strumosis is conjectural. Most ovarian strumas store but little iodine. The storage does not parallel morphologic changes.

**Carcinoma of Ovary.**—Pemberton presents an analysis of 149 ovarian cancers encountered among 855 patients with ovarian tumors treated between 1906 and 1938 at the Free Hospital for Women. Four of the cancers were found in women between 26 and 30 years of age and 17, 46, 47, 28 and 7, respectively, in each progressive decade. The majority, 61 per cent, occurred between the ages of 40 and 60, average 49 years. Twenty-five, or 22 per cent, of the women were completely sterile and 15 others had had only miscarriages, substantiating Lynch's sugges-

tion that women in whom ovarian cancer develops show a reduced fertility. There was no relation between the cancer and menstrual abnormalities. Of the 149 cancers 44 were semisolid and 70 cystic serous adenopapillary carcinomas, 10 semisolid and 18 cystic pseudomucinous adenopapillary carcinomas, 6 medullary carcinomas and 1 peritoneal pseudomyxoma. At operation all but 3 were designated as bilateral (58) or unilateral (88). Enough ascites to be noted on the operative record existed in 71 of the patients. The tumors were described as adherent to other organs in 121 instances. In 36 per cent the extent (metastasis) of the disease precluded cure, indicating the necessity of earlier diagnosis, which is to be had only by preventive examinations. The serous cancers were somewhat more malignant than the pseudomucinous tumors. The medullary carcinomas are insidious; they become adherent and grow without symptoms. Only 2 of the 6 patients noticed some swelling; the only complaint of the others was abdominal discomfort. Six metastasized to the endometrium. Because of metastasis and the frequent occurrence of bilateral growths, removal of both tubes and ovaries and hysterectomy is indicated whenever possible. Of 37 patients with semisolid serous adenopapillary carcinoma operated on five or more years ago, only 1 is living (six and a half years); 22 of the 31 who survived the operation died within two years, 4 within three years, 2 within four years, 1 in eight years and 1 in 28 years. These 2 last patients, who died of other causes than cancer, and the living patient show that apparently only 3 of 37 patients were cured by treatment. More optimism is seen among the 53 patients with cystic serous adenopapillary cancers operated on five or more years ago; 6 are untraced, 2 died postoperatively, 26 died within one to fourteen years after operation, 16 are living and well from five to twenty years after operation and 3 are living with the disease from five to fifteen years after the operation. Of 24 patients with pseudomucinous adenopapillary cancers 1 is untraced, 16 died within one and fifteen years and 7 are living and well from five to sixteen years after operation. Only 1 of the 12 patients surviving more than five years had a semisolid tumor. Of the 114 patients discussed 37, or 32 per cent, lived five or more years after operation. The author feels that because such a large proportion (47 per cent) die within the first two years after operation it might save a patient a useless operation and convalescence if she was not operated on if the peritoneoscope showed generalized abdominal metastases. However, such patients have nothing to lose, and operation may prolong life of a few.

**Cancer of Vulva.**—Taussig analyzes 155 cases of vulval cancer encountered at the Barnard Free Skin and Cancer Hospital and in his private practice during the last thirty years. Except for the following the carcinomas were of the squamous type; 3 melanomas originating about the labia and urethral meatus, 12 periurethral cancers classified as vulval lesions as their exact point of origin could not be determined, 1 small labial tumor proved to be an adenocarcinoma, probably of sweat gland origin, and 3 adenocarcinomas arising from Bartholin's gland. The lesions varied from small well differentiated papillary nodules in which a positive diagnosis could be established only after careful study to tumors in which the loose-structured, undifferentiated cells resembled sarcoma. The former relatively benign lesions usually originated from the skin of the labia or prepuce and the latter from old syphilitic vestibular ulcers or from the glans of the clitoris. In 88 there was evidence of lymph gland metastasis, either as large hard fixed glands in the advanced inoperable cases or microscopic evidence in cases in which the lymphatic chain was excised. Extension of the disease to more distant lymphatics was relatively infrequent. Some of the terminal cases showed pulmonary involvement. There were 10 cases of multiple cancers that occurred either before or after the vulval carcinoma; metastasis was eliminated. The average age was 58 years. Pruritus was the most important symptom, causing 42 patients to come for examination. Other symptoms were lump, ulcer, a bloody discharge or burning on urination. Inexcusable delay in seeking medical advice was most frequent. Only 7 women sought advice within three months. The delay was often increased by failure in diagnosis or improper treatment. In spite of this, 7 such patients survived five or more years. Leukoplakic vulvitis was the etiologic factor

in almost one half of the cases. It was an underlying factor in 72 of 104 cases of epidermal (including the vulval and preputial skin) cancer. The author feels that the incidence of vulval carcinoma might be cut in half if the following measures were adopted: (1) complete vulvectomy in well developed leukoplakic vulvitis and rigid supervision in milder cases when operative treatment is refused, (2) intensive antisyphilitic treatment in tertiary lesions of the vulva, especially in Negroes, (3) removal of vulval warts in women past the menopause, (4) close observation or excision of enlarged Bartholin glands in women more than 40 years of age and (5) cautery excision or radiant treatment of urethral caruncles. He particularly stresses the advantages of surgery over nerve resection or treatment with ovarian preparations in leukoplakic vulvitis. The latter often decreases the pruritus but raises the question whether the use of carcinogenic substances may not at times predispose to the development of a cancer. Of the 155 patients, in 117, or 75.5 per cent, the tumor with or without its tributary lymph gland chain was excised. Some of the vulvectomies were only palliative procedures. About 70 per cent of vulval cancers are surgically operable. The operative mortality varied primarily with the age and physical condition of the patient rather than with the extent of the operation. There is definite evidence of the value of radical lymph gland resection. Of 74 patients seen more than ten years ago 12, or 16 per cent, survived for ten years. Of 24 patients subjected to a complete Basset operation more than ten years ago 16 survived for five years and 10 for ten years. Of the 6 who died in this second five years, 4 had recurrence of the vulvar lesion, 1 died of a new cancer originating in the breast and 1 died of acute influenzal pneumonia. Of the 10 patients who survived for ten years, only 6 are still living today. The 2 patients who have survived for the longest time were operated on sixteen and seventeen years ago, respectively.

### American Journal of Physiology, Baltimore

131:1-290 (Nov.) 1940. Partial Index

- Effect of Asphyxiation of Spinal Cord on Pain Sensibility. A. van Harreveld, Pasadena, Calif.—p. 1.
- Observations on Pressor Substance Causing Rise in Blood Pressure Following Termination of Temporary, Complete Renal Ischemia. S. D. Leo, M. Prinzmetal and H. A. Lewis, Los Angeles.—p. 18.
- Influence of Adrenalectomy and of Fasting on Intestinal Absorption of Carbohydrates. Rose Marrazzi, New York.—p. 36.
- Control of Coronary Blood Flow in Heart-Lung Preparation. E. Hausner, Amsterdam, N. Y.; H. E. Essex, J. F. Herrick and E. J. Baldes, Rochester, Minn.—p. 43.
- Cardiac Output in Rest and Work in Humid Heat. E. Asmussen, Boston.—p. 54.
- Syndrome of Polydipsia and Polyuria Induced in Normal Animals by Desoxycorticosterone Acetate. C. Ragan, J. W. Ferrebee, P. Phyfe, D. W. Atchley and R. F. Loeb, New York.—p. 73.
- Heat Exchange and Regulation in Radiant Environments Above and Below Air Temperature. C.-E. A. Winslow, A. P. Gaggie and L. P. Herrington, New Haven, Conn.—p. 79.
- Studies in Iodine Metabolism of Thyroid Gland in Situ by Use of Radio-Iodine in Normal Subjects and in Patients with Various Types of Goiter. J. G. Hamilton and M. H. Soley, San Francisco.—p. 133.
- Efferent Pathway for Reflex Pupillomotor Activity. R. Hodes, Boston.—p. 144.
- Variation in Concentration of Acids of Gastric Content in Normal Subjects Before and Following Immersion of Hand and Entire Body in Water at Various Temperatures. Grace M. Roth and M. A. Gabrielson, Rochester, Minn.—p. 195.
- Species Differences in Cholinergic Action of Estrogen. S. R. M. Reynolds and Frances I. Foster, Brooklyn.—p. 200.
- Vago-Insulin and Sympathetic-Adrenal System and Their Mutual Relationship Under Conditions of Central Excitation Induced by Anoxia and Convulsant Drugs. J. Feldman, R. Cortell and E. Gellhorn, Chicago.—p. 281.

### Archives of Physical Therapy, Chicago

21:641-704 (Nov.) 1940

- Cultivated Relaxation in "Essential" Hypertension. E. Jacobson, Chicago.—p. 645.
- Radio Interference Problems from Operation of Electromedical Apparatus. E. K. Jett, Washington, D. C.—p. 653.
- Frostbite of Extremities: Clinical and Pathologic Considerations in Its Diagnosis and Treatment. F. V. Theis, Chicago.—p. 663.
- Rheumatoid Arthritis: Etiology and Treatment. R. L. Haden, Cleveland.—p. 671.
- Treatment of Hypertrichosis by Improved Apparatus and Technique. M. H. Marton, New York.—p. 678.
- Physical Therapy in Relation to Orthopedics. T. Bagwell, Knoxville, Tenn.—p. 684.
- Electrode Position in Diathermy Treatment. B. D. Judovich and E. J. Pomerantz, Philadelphia.—p. 688.

### Archives of Surgery, Chicago

41:1305-1544 (Dec.) 1940

- Some of the Medical Centers of South America. G. G. Turner, London, England.—p. 1307.
- Physiologic Sphincter of Hepatic Bile Duct. P. L. Mirizzi, Córdoba, Argentina.—p. 1325.
- Ligation of Inferior Vena Cava. J. L. Whittenberger and C. Huggins, Chicago.—p. 1334.
- Sickle Cell Disease: Pathogenic, Clinical and Therapeutic Considerations. J. Bauer, Los Angeles.—p. 1344.
- Response of Plasma Prothrombin to Vitamin K Substitute Therapy in Cases of Hepatic Disease. J. G. Allen and O. C. Julian, Chicago.—p. 1363.
- Time Required for Blood to Flow from Arm and from Foot of Man to Carotid Sinuses: I. Effect of Temperature, Exercise, Increased Intramuscular Tension, Elevation of Limbs and Sympathectomy. L. A. Smith, E. V. Allen and W. M. Craig, Rochester, Minn.—p. 1366.
- Circulation Time from Foot to Carotid Sinus and from Arm to Carotid Sinus of Man: II. Effects of Operation and of Administration of Thyroid Gland; Postoperative Phlebitis and Pulmonary Embolism. L. A. Smith and E. V. Allen, Rochester, Minn.—p. 1377.
- \*Revascularization of Ischemic Kidney. G. de Takáts and G. W. Scupham, Chicago.—p. 1394.
- Suture Studies: New Suture. J. E. Bellas, Peoria, Ill.—p. 1414.
- Recurrence of Infection After Elective Operations in Cases of Healed Suppuration in Bones and Joints. J. B. Davis, Portland, Ore.—p. 1426.
- Recurrent Inguinal Hernias: Study of 282 Hernias and 268 Repairs. H. J. Shelley, Fort Worth, Texas.—p. 1437.
- Changes in Bones and Joints Resulting from Interruption of Circulation: II. Nontraumatic Lesions in Adults with Bone Infarction; Arthritis Deformans. D. B. Phemister, Chicago.—p. 1455.
- Familial Occurrence of Hyperplastic Gastric Polyps: Report of Two Cases; Classification of Benign Mucosal Tumors of Stomach. R. Schindler, Chicago, and F. B. McGlone, Denver.—p. 1483.
- Comparative Concentration of Human Hepatic Bilirubin and Cholesterol by Gallbladder: Postmortem Study. S. J. Lloyd, Rochester, Minn.—p. 1494.
- Review of Urologic Surgery. A. J. Scholl, Los Angeles; F. Hinman, San Francisco; A. von Lichtenberg, Budapest, Hungary; A. B. Hepler, Seattle; R. Gutierrez, New York; G. J. Thompson, J. T. Priestley, Rochester, Minn.; E. Wildholz, Bern, Switzerland, and V. J. O'Connor, Chicago.—p. 1505.

**Revascularization of Ischemic Kidney.**—De Takáts and Scupham attempted renal revascularization of 4 patients suffering from renal vascular damage. Their first patient was operated on in April 1936, at which time muscle flaps were sutured around the decapsulated and scarified kidney on both sides. Since that time 2 more patients have had a similar unilateral operation, and in another patient omentum was used to cover the kidney. In no patient was there a definite improvement. The condition of the first patient was classified as benign nephrosclerosis because of the absence of retinal hemorrhages and exudates; definite impairment of renal function was present. The urea clearance and urea ratio have not changed appreciably for four years nor has the heart shown any deterioration. The vascular encephalopathy (fleeting paralysis of the arm) has progressed to hyperactive reflexes, headaches, papilledema and blurred vision, and now after repeated strokes mental deterioration is in its terminal stage and will most likely be the cause of death. Neither renal function tests nor nitrogen retention showed any deterioration of renal function while the cerebrovascular episodes were recurring. The authors feel that the process in this case has not been influenced, although renal impairment has not progressed since the operation. The malignant nephrosclerosis in the patient for whom the omentum was used obviously carried the worst possible prognosis. He died ten months after the operation, with gradual failure of his cardiovascular and renal systems. The third patient was a 7 year old child with juvenile malignant nephrosclerosis in conjunction with congenital hypoplasia of one kidney. The anomalies consisted of unilateral hypoplasia, absence of cortical tissue with development of blind subcapsular diverticula communicating with the pelvis of the kidney and cystic spaces filled with colloid material. The authors believe that, if pediatricians habitually recorded blood pressures, juvenile malignant hypertension might be recognized earlier. The removal of a hypoplastic kidney before the other kidney suffers vascular damage seems logical. In their case the microscopic picture of the large compensatory kidney could not be distinguished from that of the hypoplastic one. Nephrectomy of the atrophic kidney might have been curative within the first few months after the onset of symptoms, two years before admission to the hospital. The unilateral decapsulation and application of a muscle flap did not arrest the disease, which ended in cardiac failure. The fourth patient was a woman of 32 suffering from lupus erythematosus, unilateral

renal disease and hypertension. She was subjected to an exploratory procedure and lumbar sympathectomy, and a left renal vascularization was performed. She died six days after the operation. The cause of death was not determined. Biopsy revealed nephritis.

### California and Western Medicine, San Francisco

53:201-252 (Nov.) 1940

- \*Primary Carcinoma of Lung: Importance of Early Diagnosis in Increasing Operability and Curability. P. C. Samson, Oakland, and E. Holman, San Francisco.—p. 208.
- Immediate Management of Surface Injuries. G. B. O'Connor, San Francisco.—p. 211.
- Interpretation of Laboratory Examinations in Diagnosis of Infectious Diseases. C. S. Keefer, Boston.—p. 214.

**Primary Carcinoma of Lung.**—Samson and Holman performed six total pneumonectomies for primary pulmonary carcinoma, with postoperative recovery of 4 patients. In neither of the 2 fatal cases was death due to operative shock. These 2 patients survived eleven and twenty-four days, with death resulting from purulent pericarditis and empyema, respectively. In both fatalities the pneumonectomy was on the right side. It is the authors' impression that adequate closure of the stern bronchus is more difficult on the right, owing to the relatively higher origin of the right upper lobar bronchus. In addition, mediastinal shift to the right and compensatory hypertrophy of the left lung do not take place as easily as do the corresponding mechanisms for obliteration of the left pleural cavity. Of the four postoperative recoveries 1 patient died a year later from coronary thrombosis and 1 in eight months from cerebral metastasis. Two patients are living. As with carcinoma elsewhere in the body, early diagnosis is paramount if surgery is to be effective. Thorough roentgen studies and bronchoscopy are invaluable aids in establishing a diagnosis.

### Florida Medical Association Journal, Jacksonville

27:213-268 (Nov.) 1940

- Management of the Breast Fed Baby, Including Immunization Procedures. L. von Meyensbug, Daytona Beach.—p. 229.
- Climate and Altitude in Treatment of Hypertension and Myocardial Failure. D. P. Bird, Lakeland.—p. 233.
- Uterus Bicornis Unicollis. J. W. Snyder, Miami.—p. 236.
- Cooperative Roentgenotherapy. C. M. Gray, Tampa.—p. 240.
- Role of Unrecognized Typhoid Carrier in Transmission of Typhoid Infection. H. B. Smith, Tavares.—p. 242.

### Illinois Medical Journal, Chicago

78:377-464 (Nov.) 1940

- Transurethral Approach to Diagnosis and Treatment of Infections of Seminal Vesicles. R. H. Herbst and J. W. Merricks, Chicago.—p. 393.
- Chemistry of the Sulfonamides. P. T. Maher, Chicago.—p. 397.
- Therapeutic Applications of Sulfanilamide and Allied Compounds. E. M. K. Geiling, Chicago.—p. 404.
- Practical Application of Sulfuramids to Otolaryngology. G. J. Greenwood, Chicago.—p. 410.
- Sulfanilamide in Ophthalmology. H. W. Woodruff, Joliet.—p. 418.
- Clinical Applications of Testosterone Propionate. M. Kern, Chicago.—p. 420.
- Prostigmine in Treatment of Peripheral Circulatory Disturbances. S. Perlow, Chicago.—p. 424.
- Lactation and Involution. R. R. Loar, Bloomington.—p. 428.
- Use of Seconal as Analgesic Agent During Labor. W. G. Cummings, Evanston.—p. 431.
- Effect of Various Factors on Blood Loss in Labor Under Sodium Alurate Analgesia. M. J. O'Connell, Chicago.—p. 433.
- Prevention of Contact Infections in Children. N. T. Welford, La Grange.—p. 435.
- Oxyuriasis as Etiologic Factor of Appendicitis. J. H. Kaplan, Rockford.—p. 441.
- When Hearing Aids Should Be Used. A. A. Hayden, Chicago.—p. 442.
- Maintenance Treatment of Pernicious Anemia with Parenteral Liver Extract. H. L. Alt, Chicago, and R. H. Young, Evanston.—p. 444.
- Diagnosis and Treatment of Syphilis in Infancy and the Teen Age. F. E. Senear, Chicago.—p. 448.

### Iowa State Medical Society Journal, Des Moines

30:509-564 (Nov.) 1940

- Trouble Shooting. M. F. Jones, New York.—p. 509.
- Precipitability and Specificity of Certain Fractions of Monilia Albicans. A. P. McKee, Iowa City.—p. 516.
- Management of Minor Industrial Injuries. D. C. Conzett, Dubuque.—p. 523.
- Early Diagnosis of Carcinoma of Colon. M. Hanchett, Council Bluffs.—p. 526.
- Streptococcal Infections. R. D. Bernard, Clarion.—p. 529.
- Use and Abuse of Digitalis. G. B. Crow, Burlington.—p. 533.
- Carotid Sinus. Erma A. Smith, Ames.—p. 538.

### Journal of Experimental Medicine, New York

72:479-622 (Nov.) 1940

- Hemoglobin and Plasma Protein: Simultaneous Production During Continued Bleeding as Influenced by Diet Protein and Other Factors. Frieda S. Robschtein-Robbins, S. C. Madden, A. P. Rowe, A. P. Turner and G. H. Whipple, Rochester, N. Y.—p. 479.
- Tissue Specificity of Brain and Medullated Nerves as Shown by Passive Anaphylaxis in Guinea Pigs. G. H. Bailey and R. E. Gardner, Baltimore.—p. 499.
- Electrophoretic Studies on Elementary Bodies of Vaccinia. T. Shedlovsky and J. E. Smadel, New York.—p. 511.
- Observations on Mixtures of Elementary Bodies of Vaccinia and Coated Colloid Particles by Means of Ultracentrifugation and Electrophoresis. J. E. Smadel, E. G. Pickels, T. Shedlovsky and T. M. Rivers, New York.—p. 523.
- Union in Vitro of Papilloma Virus and Its Antibody. W. F. Friedewald and J. G. Kidd, New York.—p. 531.
- Mechanism by Which Experimental Nephritis Is Produced in Rabbits Injected with Nephrotoxic Duck Serum. C. F. Kay, Baltimore.—p. 559.
- Experimental Encephalitis: Some Factors Affecting Infection with Certain Neurotropic Viruses. L. S. King, Princeton, N. J.—p. 573.
- Recovery from Patients with Acute Pneumonitis of Virus Causing Pneumonia in Mongoose. J. M. Weir and F. L. Horsfall Jr., New York.—p. 595.
- Placental Transmission of Antibodies in Skin Sensitive Type of Human Allergy. W. B. Sherman, S. F. Hampton and R. A. Cooke, New York.—p. 611.

### Journal Industrial Hygiene & Toxicology, Baltimore

22:381-426 (Nov.) 1940

- \*Experimental Studies on Ingestion of Lead Compounds. R. A. Kehoe, J. Cholak, D. M. Hubbard, K. Bambach, R. R. McNary and R. V. Story, Cincinnati.—p. 381.
- Correlation Coefficient Between Basophilic Aggregation Test and Lead in Urine. S. F. Meek, G. R. Collins and G. C. Harrold, Detroit.—p. 401.
- Control of Tuberculosis: II. Pulmonary Tuberculosis in Employees. Ada Chree Reid, New York.—p. 408.
- Determination and Recording of Carbon Disulfide and Hydrogen Sulfide in Viscose-Rayon Industry. G. M. Reece, B. White and P. Drinker, Boston.—p. 416.

**Ingestion of Lead Compounds.**—According to Kehoe and his co-workers, data exist which indicate that within certain limits an approximate balance exists between lead absorption and lead excretion of men subject to occupational lead exposure. They have carried out a series of experiments in which lead in known quantities was administered regularly to normal subjects during which their daily lead intake in food and beverages and the daily output in the feces and urine were estimated. To maintain the induced lead exposure within safe limits, its dosage was kept below that previously found toxic for experimental animals and the dosage regarded as dangerous in industry. After a preliminary period of twenty-eight days of clinical and experimental study which demonstrated the existence of a satisfactory state of health and physiologic reactivity, one young man was started on 1 mg. daily of lead acetate. The experiment has been continued over a period of almost three and one half years. A second subject began taking a daily dosage of 2 mg. in a similar manner for fifteen months. Every week during the study each subject was given a physical examination, a complete microscopic blood and blood lead examination. Blood smears were made daily for counts of stippled erythrocytes and reticulocytes. No clinical evidence of the slightest harmful effect has been recognized by either subject or has been detected by the examinations. Both subjects have had intercurrent respiratory infections of minor severity which ran their normal course. One of them had a typical attack of food poisoning with diarrhea and vomiting, with recovery in three days. No appreciable changes in the lead metabolism occurred at this time. A faint but definitely punctate blue deposit developed at the margin of a central incisor in this subject. When the lesion was evacuated and treated, the deposit disappeared promptly. The other subject has not developed any gingival discoloration despite a slight gingivitis which has varied in accordance with care of his teeth. The authors conclude that: 1. The largest proportion of lead ingested by normal persons, with food or otherwise and whether in soluble or insoluble form, is eliminated in the feces without absorption. 2. Prolonged daily ingestion of lead in excess of 1 mg. by healthy adults is not only compatible with normal health and well being but is associated with such an increase in the elimination of lead as to result only in a slight and almost negligible retention. 3. The daily ingestion of slightly more than 2 mg. of lead for more than one year failed to cause any demonstrable effect on the health or well-being of a healthy

adult. It induced a level of lead elimination higher than that caused by the daily ingestion of 1 mg. and a slightly greater lead retention. 4. Maintained concentrations of 0.06 to 0.07 mg. of lead per hundred grams of blood over periods of months are entirely compatible with normal health and well-being. 5. Concentrations of lead in the urine from 0.05 to 0.15 mg. per liter are compatible likewise with normal health and well-being of adults. 6. The lead ingested in food and beverages by adult citizens in various parts of the United States varies from less than 0.1 mg. to more than 2 mg. with a mean daily value of approximately 0.32 mg. 7. The foregoing studies appear to show that there is a sufficient factor of safety in relation to the lead content of the general food materials in the United States.

### Journal of Nutrition, Philadelphia

20:413-518 (Nov.) 1940. Partial Index

- Relation of Pantothenic Acid to Filtrate Fraction of Vitamin B Complex. Mildred K. Dimick and A. Lepp, Emeryville, Calif.—p. 413.  
Comparison of Nutritive Values of Raw, Pasteurized and Evaporated Milks for the Dog. H. D. Anderson, C. A. Elvehjem and J. E. Gonce Jr., Madison, Wis.—p. 433.  
Influence of Lactose on Calcium Retention in Children. Rosalind Mills, Herta Breiter, Elizabeth Kempster, Beula McKey, Marjorie Pickens and Julia Outhouse, Urbana, Ill.—p. 467.  
Effect of Pyrazine Acids and Quinolinic Acid on V Factor Content of Human Blood and on Canine Blacktongue. W. J. Dann, H. I. Kohn and P. Handler, Durham, N. C.—p. 477.  
Placental and Mammary Transfer of Vitamin E in the Rat. K. E. Mason and W. L. Bryan, Nashville, Tenn.—p. 501.

### Journal of Pediatrics, St. Louis

17:571-708 (Nov.) 1940

- Correction of Distorted Fluid Equilibrium in Presence of Vascular Injury. A. S. Minot and Katharine Dodd, Nashville, Tenn.—p. 571.  
\*Value of Bacillus Pertussis Vaccine in Prevention of Whooping Cough in a Child-Caring Institution. J. M. Lewis, L. H. Bärenberg, L. Greenspan and B. Greenberg, New York.—p. 585.  
Comparative Nutritive Efficiency of Intravenous Amino Acids and Dietary Protein in Children with Nephrotic Syndrome. L. E. Farr, K. Emerson Jr. and P. H. Futcher, New York.—p. 595.  
\*Vitamin K in Hemorrhagic Disease of the Newborn Infant. C. E. Snelling, with technical assistance of Winnifred Nelson, Toronto.—p. 615.  
Concentration of Ascorbic Acid in Plasma During Treatment of Infantile Scurvy. R. L. Mindlin, Boston.—p. 621.  
\*Intracutaneous Vaccination Against Smallpox by Means of Chick Embryo Culture Virus. L. Jacobs, New York, and H. Orris, Hillside, N. J.—p. 626.  
Formolized Vaccinia Virus: Results of Its Use with Children Who Had Never Been Vaccinated Previously. H. H. Donnelly, Washington, D. C., and A. J. Weil, Pearl River, N. Y.—p. 639.  
Rocky Mountain Spotted Fever: Analysis of Eighteen Cases in Children. H. A. Ong, Washington, D. C., and J. F. Raffetto, Asbury Park, N. J.—p. 647.  
Peptic Ulcer in Children: Report of Ten Cases. W. F. Burdick, Washington, D. C.—p. 654.  
Massive Unilateral Pulmonary Fibrosis Due to Obstructive Tracheobronchial Tuberculosis. P. E. Rothman and R. Mapes, Los Angeles.—p. 659.  
Diphtheria Treated Unsuccessfully with Sulfonamide Compounds: Report of Two Fatal Cases. S. M. Abelson and H. Leichenger, Chicago.—p. 670.  
An Easy-To-Make Infant Incubator. G. H. Hess, Bisbee, Ariz.—p. 672.

**Vaccine Prophylaxis of Whooping Cough.**—Lewis and his associates present the following data bearing on the value of *Bacillus pertussis* vaccine: In an institution, 77 children from 15 months to 4 years who had been inoculated with *Bacillus pertussis* vaccine (Sauer) and 70 children who were not inoculated were intimately exposed to whooping cough under comparable conditions. Whooping cough developed in 24 of the inoculated children, whereas 58 of the uninoculated children were attacked. The disease was definitely less severe in the inoculated group. Three different dosages of the vaccine were employed; 80, 110 and 130 billion organisms. The incidence of whooping cough was 20 per cent among those receiving 130 billion organisms as compared to 57 per cent in the other two groups. From four months to four years prior to the epidemic 271 children were discharged from the institution. One hundred and twenty of these had been inoculated with 80 billion organisms at the institution and 151 had not been inoculated. The ages and time elapsed since discharge were comparable for the two groups. Two, or 1.7 per cent, of the inoculated children have since contracted whooping cough as compared to 22, or 14.6 per cent, of the control children. The high degree of effectiveness of the 80 billion dosage among these children was probably due to the fact that the exposures were not intensive.

Under conditions of household exposure, the 80 billion dosage frequently does not prevent whooping cough although it may modify the course of the disease. Household exposure may be compared to that which existed in the institution and therefore it is probable that the 130 billion dosage would prove more effective among the intimately exposed children.

**Vitamin K for Neonatal Hemorrhagic Disease.**—Snelling and Nelson determined the bleeding, clotting and prothrombin time of 11 cases of hemorrhagic disease of the newborn before and after arresting the hemorrhage by various methods of treatment. The prothrombin times varied from one hundred and sixty seconds to no clot formation, and the bleeding and clotting times were elevated. After treatment when the bleeding had ceased the prothrombin time was ninety-five seconds or less and the bleeding and clotting times were within normal limits. The authors' experience for a previous five years with 64 cases shows that 12 required more than one transfusion to effect a cure. One patient received one transfusion and was still bleeding twelve hours later with only partial diminution of the prothrombin time. A second transfusion effected a cure. Another patient received a transfusion and was given natural vitamin K by mouth and a second transfusion was necessary. A third patient was cured with one transfusion and 4 cc. of vitamin K by mouth. The prothrombin time of another patient was lowered by natural vitamin K by mouth. Vitamin K by mouth is probably effective, but the possibility of its not being retained or of lack of absorption makes it an unsafe procedure. Six cases of hemorrhagic disease were treated with synthetic vitamin K (2 methyl 1-4 naphthoquinone) intravenously. The prothrombin time was decreased by the vitamin K; in 4 the bleeding stopped, in 1 case the authors felt it was because external bleeding had ceased and in their first case to be treated they did not have the courage to wait longer than one hour without administering blood. None of the babies showed any ill effects as a result of the intravenous administration of the synthetic vitamin K. In the first 2 of the 5 cases treated with vitamin K the bleeding was arrested with the hemoglobin at a normal level. In the other 3, although the bleeding was arrested, the patients were handicapped by low hemoglobin, and transfusion was given twenty-four hours after admission. This is most important because, although bleeding may be arrested with vitamin K it is also necessary to restore the hemoglobin to a normal level. The authors recommend that a hemoglobin estimation be done in hemorrhagic disease of the newborn and if decreased that vitamin K be administered intravenously with a transfusion, but that if the hemoglobin is normal only vitamin K be given. In their experience vitamin K and transfusion does away with the necessity of second transfusions.

**Intracutaneous Vaccination Against Smallpox.**—Jacobs and Orris studied the reactions among the residents of the poorer crowded tenement districts of New York City following the intracutaneous inoculation of chick embryo vaccine virus against smallpox. All races, colors and creeds were represented. Infants and children from 6 months to 5 years of age were in the majority, but some older children and even adults were followed for comparison and study. More than 800 infants and children were vaccinated with 0.1 cc. of chick embryo culture virus and after from six to thirty months later complete follow-up observations after dermal revaccination with Department of Health cowpox of only 290 was possible. Of 102 initially vaccinated with 0.1 cc. culture virus mixed with blood serum from donors previously vaccinated against smallpox, there were 33.3 per cent primary takes, 50 per cent accelerated takes and 16.7 per cent immune reactions. Of 137 originally vaccinated with 0.1 cc. culture virus mixed with blood serum from nonvaccinated donors, there were 10.2 per cent primary takes, 70.1 per cent accelerated takes and 19.7 per cent immune reactions. Of 42 initially vaccinated with two simultaneous injections of 0.1 cc. of pure culture virus or mixed with human blood serum from nonvaccinated donors, there were 4.8 per cent primary takes, 52.3 per cent accelerated takes and 42.9 per cent immune reactions. These two injections resulted in the highest (95 per cent) degree of immunity. It is seen that the activity of the virus is diminished if the human serum with which it is mixed has come from previously vaccinated donors. Intracutaneous vaccination with the culture virus may be done rapidly

and efficiently by the average physician. The reactions are characteristic and may be readily recognized. The course of vaccination is benign. Systemic reactions are rare. A minute scar may result in a few persons. The method appears to be the one of choice. After a lapse of about two years, revaccination with culture virus or cowpox should be made.

### Kansas Medical Society Journal, Topeka

41:409-452 (Oct.) 1940

- Role of Surgery in Painful Feet. E. D. McBride, Oklahoma City.—p. 409.  
Clinical Approach to the Migraine Problem: Part I. General Consideration and Data. D. V. Conwell and C. J. Kurth, Halstead.—p. 413.  
Id.; Part II. Preventive Treatment. D. V. Conwell, Halstead.—p. 415.  
Tuberculosis Case Finding in University of Kansas Students. R. I. Canuteson, Lawrence.—p. 417.  
X-Ray Interpretation in Tuberculosis Case Finding. G. M. Tice, Kansas City.—p. 420.  
Prolapse of Intervertebral Disk. F. A. Carmichael Jr., Kansas City, Mo.—p. 422.  
Tularemia Complicated by Septicemia and Heart Disease. D. Stump and F. Quinn, Kansas City.—p. 426.

### Medical Annals of District of Columbia, Washington

9:371-412 (Nov.) 1940

- Importance of Cardiovascular-Renal Diseases: Statistical Review. P. Shepherd, Newark, N. J.—p. 371.  
Importance of Heart Disease: Cardiovascular Situation Today, Present and Probable Future Trends. L. S. Ylvisaker, Newark, N. J.—p. 383.  
Diagnosis and Treatment of Heart Wounds: Summary of Thirty-Four Cases. I. A. Bigger, Richmond, Va.—p. 390.  
Case Reports by William Stokes of Dublin. W. B. Daniels, Washington.—p. 395.

### Missouri State Medical Assn. Journal, St. Louis

37:491-526 (Dec.) 1940

- Importance of Water Balance and Electrolytes in Preoperative and Post-operative Care of Surgical Cases. G. V. Post, Chicago.—p. 491.  
Cardiology: Review of a Decade. J. Jensen, St. Louis.—p. 494.  
Diagnosis of Renal Lesions. I. H. Lockwood and A. B. Smith, Kansas City.—p. 498.  
Addison's Disease. R. E. Myers, Joplin.—p. 502.  
Meniscus Cyst of Knee Joint. J. Kulowski, St. Joseph.—p. 503.

### New England Journal of Medicine, Boston

223:789-834 (Nov. 14) 1940

- \*Syphilitic Aortitis as Cause of Sudden Death. T. Leary, Boston.—p. 789.  
\*Instantaneous "Physiologic" Death. S. Weiss, Boston.—p. 793.  
\*Sudden Death. A. R. Moritz, Boston.—p. 798.  
Cancer of Rectum and Sigmoid. W. M. Shelden, Boston.—p. 801.  
Some Proposed Changes in the Massachusetts Law as It Relates to Medical Practice. S. Rushmore, Boston.—p. 808.  
Acquired Hypersensitivity to Sulfapyridine and Sulfamethylthiazole. A. Davidson and J. G. M. Bullova, New York.—p. 811.  
Regional Anesthesia. A. W. Squires, New York.—p. 813.

**Syphilitic Aortitis and Sudden Death.**—Leary points out that syphilitic aortitis is today the important form of cardiovascular syphilis seen by the pathologist and that several of its processes tend to lead to sudden death. In syphilitic aortitis there is overstimulation of the essential aortic blood vascular system, the vasa vasorum. With the excessive growth of blood vessels, which penetrate through the media into the intima, there is an excessive growth of fibroblastic tissue, which thickens the intima and tends to narrow and occlude the portions of the coronary arteries lying within the aortic wall. Marked narrowing or occlusion of the ostiums may result in sudden death of the coronary type in the early stages of the disease. In addition to widening of the commissures and rolling of the cusps, atherosclerosis in late syphilitic aortitis tends to be followed by calcification and diffuse dilatation of the aorta, including the ring. Dilatation of the ring produces aortic insufficiency, which may be followed by sudden death of the coronary type but usually leads to late progressive cardiac decompensation. Rupture of aneurysms is also a cause of sudden death, as is the production of local dissecting aneurysms in the lower ascending aorta, with rupture into the pericardium. Experimental atherosclerosis in the rabbit results in late diffuse dilatation of the aorta resembling that found in combined syphilitic aortitis and atherosclerosis in man.

**Instantaneous "Physiologic" Death.**—Weiss states that in his experience acute structural lesions in vital organs are often meager or absent in cases of instantaneous death. The lesions

offered as an explanation of death are usually chronic. Post-mortem examination usually fails to reveal proof of or even evidence for the cause of death. Instantaneous death is usually cardiac in origin and depends on an underlying physiologic mechanism. There is a close similarity and interrelation between the mechanism of instantaneous death and syncope; frequently instantaneous death is merely fatal syncope. Thus of 50 patients with aortic stenosis, most of those who suffered from attacks of syncope died instantaneously. Patients suffering from the Adams-Stokes type of syncope may die instantaneously during one of their attacks. The mechanisms of transient and fatal syncope are presumably similar or identical in these cases. Coronary sclerosis, myocardial hypertrophy of arterial hypertension, aortic stenosis and various types of infectious myocarditis or nutritional deficiencies predispose to syncope and to instantaneous death, for in these states the heart has a general tendency to asystole or to cardiac arrhythmias. Such cardiac dysfunction can be induced by the stimulation of various reflexes. Reflex reactions of asystole, auricular fibrillation, bundle branch block and complete auriculoventricular dissociation can be induced. At no time was ventricular fibrillation of reflex origin observed. In the presence of coronary sclerosis there is a tendency to hypersensitivity of the vagal type of carotid sinus reflex as well as of other vagal reflexes. The tonus and activity of the reflexes of the autonomic nervous system vary considerably in normal persons. Under the influence of stress and strain or of disease a remarkable degree of hyperactivity of certain reflexes can develop. This explains why in many persons the effect of emotion or chemical stimuli on the heart and vessels is slight and surgical manipulation of certain nerve structures can be done with safety, while in others alarming seizure or death ensues. The essential difference lies in the ability to reestablish normal equilibrium. The circulation in syncope is influenced markedly by gravity. Hence in the presence of a hyperirritable myocardium the orthostatic position during syncope becomes a serious threat to the patient's life. Thus pleural, pericardial or abdominal tap in patients with myocardial disease is more apt to lead to instantaneous death in a sitting position than in a recumbent one. Patients with an ischemic myocardium or with hyperactive vagal reflexes are apt to die instantaneously during the strain of defecation. Instantaneous death is prone to develop in either young or old after exertion if the vital reflexes and the myocardium are irritable. Instantaneous death may occur during a volatile anesthesia, angina pectoris and coronary thrombosis. In the presence of ischemic myocardium and hyperactive reflexes, fright or other emotional stress may induce cardiac arrhythmia, syncope and death. Although ventricular fibrillation may occur unexpectedly and usually causes syncope, this arrhythmia plays but a minor part in unexpected states of unconsciousness. Asystole occurs more frequently than ventricular fibrillation in the usual types of death due to infectious or degenerative diseases.

**Sudden Death.**—Moritz discusses sudden death as it pertains to the medical examiner. He divides the cases into three types: instantaneous deaths, unexpected syncope with deepening unconsciousness terminating in death, and rapidly fatal illnesses with early prostration but not ushered in by unconsciousness. In instantaneous deaths, cardiac standstill occurs simultaneously with collapse. Death results from cardiac inhibition and apparently depends on constitutional or acquired neurocirculatory instability. The initiating stimulus may be excitement, fear, anxiety or other intense emotional disturbances. A minor physical injury or the induction of anesthesia may precipitate collapse. The so-called thymicolymphatic death of infants and children may depend on the existence of a hyperirritable cardioregulatory mechanism. Instantaneous death may and occasionally does occur in persons with no recognizable heart disease. In the second type of sudden deaths, minutes or even hours may intervene between syncope and death. Heart disease is usually the cause, and coronary sclerosis with or without thrombosis is pre-eminent. Any type of developmental, degenerative or inflammatory heart disease may predispose to sudden death. Circulatory failure is the most frequent cause of sudden loss of consciousness terminating in death, but the seizure may result from intracranial disturbances independent of heart failure. Of these, hemorrhage (as in cerebral apoplexy, congenital aneurysm and

brain tumors), either within or around the brain, deserves first consideration. Less common intracranial causes include arterial thrombosis or embolism, meningitis, encephalitis and the sudden development of edema in the vicinity of a tumor or abscess. Diabetic acidosis, uremia and acute adrenal insufficiency are also occasional causes of sudden death. In the third type of sudden death, loss of consciousness is not the first manifestation of the fatal seizure. Disability terminating in death in these cases may progress with such great rapidity that the victim is likely to be found unexpectedly dead in bed. Any of the causes already described may operate in this manner. Fulminating infection, particularly in the very young or the very old, is likely to progress with such rapidity that the entire clinical course of the disease may occur within a few hours. Many unexpected deaths of young infants attributed to suffocation or to status thymico-lymphaticus are actually due to infection. It is not unusual for an old person thought to be well in the evening to be found dead in bed the next morning as a result of bronchitis, pneumonia or peritonitis. In such circumstances circulatory failure undoubtedly plays an important part. Hemorrhage is another cause of unexpected prostration progressing rapidly to death. Fatal bleeding into the pleural, peritoneal cavity or into the lumen of the intestine, aneurysm, tumor, varix, ulcer and ectopic pregnancy are common causes of a concealed fatal hemorrhage. The entrance of a few ounces of blood into the air passages may cause the victim to drown in his own fluid. Common causes of intrabronchial bleeding include aortic aneurysm, tumor, abscess and tuberculosis of the lungs. The medical examiner must decide which cases of sudden or obscure death shall be investigated, so that deaths from unnatural causes shall not be overlooked.

### Pennsylvania Medical Journal, Harrisburg

44:129-256 (Nov.) 1940

- Complications Incident to Paranasal Sinusitis. F. W. White, New York.—p. 141.
- Diabetes: VII. Management of Pregnancy in Diabetes. R. D. Porter, Jenkintown.—p. 148.
- Tularemic Pneumonia: Its Recognition and Prevention. H. B. Thomas, York.—p. 151.
- Basal Metabolic Rate in Various Diseases. E. R. Janjigian, Danville.—p. 157.
- Primary Acute Pneumococcal Peritonitis: Report of Case Treated with Sulfapyridine. N. C. McCollough, Butler.—p. 159.
- \*Comparison of Therapeutic Agents in Treatment of Scarlet Fever. P. F. Lucchesi and B. B. Stein, Philadelphia.—p. 162.
- Law and Lunacy. B. L. Keyes, Philadelphia.—p. 165.
- Pneumococcal Meningitis with Reference to Sulfapyridine Therapy. D. Turnoff, E. B. Marenus and T. G. Schnabel, Philadelphia.—p. 172.
- \*Rocky Mountain Spotted Fever in Southeastern Pennsylvania. W. P. Havens, C. G. Whitbeck and Cecelia G. Kramer, Philadelphia.—p. 176.
- Mechanism of Postmetrazol Gibbus. T. K. Rathmell, Norristown.—p. 180.
- Cardiac Thrombi Complicating Mitral Stenosis with Pulmonary Tuberculosis in a Miner. S. C. Stein, White Haven, and J. F. Giering, Wilkes-Barre.—p. 183.
- Diagnosis and Treatment of Pelvic Endometriosis. F. L. Payne, Philadelphia.—p. 186.
- Clinical Uses of Paredrine Hydrobromide in Eye. I. S. Tassman, Philadelphia.—p. 191.
- Neurologic Problems Past Fifty. M. T. Moore, Philadelphia.—p. 195.
- Evaluation of Biologic Products in Treatment of Pertussis. P. F. Lucchesi and N. Gildersleeve, Philadelphia.—p. 202.
- Bladder Neck Obstruction in Female. W. Baurys, Nanticoke.—p. 206.

**Therapeutic Agents for Scarlet Fever.**—Lucchesi and Stein compared the effect on fever and complications of four types of treatment given 1,780 patients with scarlet fever. Five hundred and nineteen patients, 164 of whom were mildly and 355 moderately ill, were treated symptomatically and served as controls. Of the remaining patients 581 (12 mildly, 251 moderately and 318 severely ill) received scarlet fever antitoxin, 492 patients (in 53 of whom the disease was mild, 321 moderate and 118 severe) were treated with foreign protein (diphtheria antitoxin) and 188 patients (20 were mildly, 105 moderately and 63 severely affected) were given convalescent scarlet fever serum. The patients given the antitoxin had the shortest period of fever, five and forty-nine one-hundredths days as compared to six and four-tenths days for the control group and six and six one-hundredths and seven and one-tenth days respectively for those receiving foreign protein and convalescent serum. The highest complication rate, 23.94 per cent, occurred among the patients receiving convalescent serum; the rates for the other three groups were respectively 17.73, 20.65 and 21.95 per cent. The figures indicate the average complication rate for mild, moderate and severe cases. For the moderately ill patients the

highest complication rate (21.13 per cent) occurred among the control group and the lowest (17.53 per cent) among those receiving antitoxin. Otitis media and adenitis were the most frequent complications in all four groups. The incidence of serum disease for the patients receiving antitoxin was 38.7 per cent and for those given foreign protein 28.02 per cent. The difference is probably due to the larger volume of scarlet fever antitoxin given with each therapeutic dose. The use of ephedrine and ephedrine and calcium for the prevention of serum disease had no beneficial effect on the patients treated with antitoxin; the incidence was even higher among those receiving the drugs. Patients receiving foreign protein experienced a negligible response from ephedrine and calcium and a moderate response from ephedrine.

### Rocky Mountain Spotted Fever in Pennsylvania.

According to Havens and his associates, spotted fever is at present endemic in at least forty-two of the forty-eight states, and since 1931 it has been reported in twenty-six of the Central and Eastern states. Although its recognition in the East has been recent, it is now believed that spotted fever has been endemic in the Eastern and Central states as long as in those farther west. During the spring and summer of 1939, 13 cases occurred within 30 miles of Philadelphia. Exact data could not be obtained in most of them, and it is uncertain whether each actually was a case of spotted fever. However, many more cases may have occurred but because of their mildness were not detected or reported. Because of the widespread interest in the disease the authors attempted to determine roughly what percentage of ticks in the environs of Philadelphia harbor the infection. As recent engorgement of blood is required to reactivate the virus, engorged ticks were collected by volunteers from dogs roaming the woods and fields. Eighteen lots of material from four hundred ticks obtained from eighteen different localities were injected into sets of 2 guinea pigs each. Only 1 lot appeared to be infected with the causative rickettsia, which represents approximately the proportion of infected ticks found by others elsewhere. Because of this apparently low rate of infectivity the authors feel that there need be no undue alarm over the contagion of spotted fever in the spring or summer months, provided reasonable care is taken to keep ticks off the body. Engorged ticks should not be plucked from animals without adequate precaution. They believe that the presence in Pennsylvania of a form of spotted fever different from that found in the West argues against the belief that the disease was brought here by cattle or rabbits transported from the West. Evidence favors the view that the disease is perennially endemic wherever rodents and ticks reside.

### Philippine Medical Association Journal, Manila

20:441-504 (Aug.) 1940

- Regional Ileitis (Crohn's Disease): Case Report. A. Liboro and D. E. Nieva, Manila.—p. 441.
- Pathologic Report of Case of Regional Ileitis. L. Gomez, Manila.—p. 449.
- Comparative Study of Some Treatments of Inflammation of Maxillary Antrum. C. D. Ayuyao, C. V. Yambao and P. Simuangco, Manila.—p. 451.
- Blood Pressure of Filipino School Children. Isabel Ferrer, Manila.—p. 457.
- Cerebral Type of Malaria: Report of Case. M. Quisumbing Sr., San Pablo, Laguna.—p. 461.
- Sulfapyridine in Treatment of Pneumococcal Pneumonia. A. H. Rivera and Andrea Naguiat, Del Carmen, Pampanga.—p. 465.

20:505-566 (Sept.) 1940

- Chronic Appendicitis: Study of Its Clinical and Pathologic Diagnosis. J. R. Estrada and S. C. Meñez, Manila.—p. 505.
- New Light on Anthelmintic Action of Santonin from Experimental Standpoint. R. Guevara, A. J. Damian and V. Uyenco, Manila.—p. 513.
- Role of Ophthalmology and Otolaryngology in Solution of Some Problems of Internal Medicine. G. de Ocampo, Manila.—p. 523.

### Physiological Reviews, Baltimore

20:469-616 (Oct.) 1940

- Mechanism of Acquired Immunity in Infections with Parasitic Worms. W. H. Taliaferro, Chicago.—p. 469.
- Pituitary-Adrenocortical Relationship. H. G. Swann, Chicago.—p. 493.
- Recent Advances in Chemistry of Calcification. M. A. Logan, Boston.—p. 522.
- Fat Absorption and Its Relationship to Fat Metabolism. A. C. Frazer, London, England.—p. 561.
- Fluoride Intoxication. D. A. Greenwood, Chicago.—p. 582.



## FOREIGN

An asterisk (\*) before a title indicates that the article is abstracted below. Single case reports and trials of new drugs are usually omitted.

**British Journal of Dermatology and Syphilis, London**

52:289-320 (Oct.) 1940

Generalized Scleroderma and Dermatomyositis: Histologic Comparison. W. Freudenthal.—p. 289.

Biochemical Aspects of Dermatomyositis. W. J. Griffiths.—p. 295.

Reticuloendotheliosis and Normoblastosis. F. S. P. van Buchem and T. Botman.—p. 304.

**British Journal of Ophthalmology, London**

24:541-580 (Nov.) 1940

Metastatic Carcinoma of Iris: Clinically Simulating Gumma. H. B. Stallard.—p. 541.

Trachoma (Some Experimental Data with Clinical Interest from Records of Combined Etiologic Investigation by Various Members of the Government Ophthalmic Hospital, and the King Institute of Preventive Medicine, Madras, 1935, 1936, 1937). R. E. Wright.—p. 547.

Preliminary Note on Use of Retrobulbar Procaine Anesthesia for Relief of Intractable Ocular Pain. L. H. Savin and T. M. Tyrrell.—p. 560.

Convergence Weakness. O. G. Morgan.—p. 564.

New Knife for Doing Van Millingen's Grafting Operation. S. Kamel.—p. 567.

**British Journal of Radiology, London**

13:357-392 (Nov.) 1940

Action of Radiations Emitted by (1) Radium Plaques, (2) Unfiltered and Filtered Radon Seeds and (3) Intravenous Injection of Radon Dissolved in Blood. A. Eidinow.—p. 357.

Some Experiments on Biologic Effects of Fast Neutrons. L. H. Gray, J. C. Mottram, J. Read and F. G. Spear.—p. 371.

Note on Dosage Data for Radium Therapy. T. H. Oddie.—p. 389.

**British Medical Journal, London**

2:545-582 (Oct. 26) 1940

\*Diagnostic Value of Pregnanliol Excretion in Pregnancy Disorders. C. L. Cope.—p. 545.

Effect of Repeated Intravenous Injections of Bilirubin on Erythropoiesis in Anemic Dogs. R. R. Bomford.—p. 549.

Dual (Kiss) Cancer of Stomach: Case. E. W. Thomas.—p. 552.

Psychiatric Casualties in London, September 1940. G. Pegge.—p. 553.

\*Treatment of Anemia by Transfusion of Concentrated Suspensions of Red Cells. D. H. G. MacQuaide and P. L. Mollison.—p. 555.

**Diagnostic Value of Pregnanliol Excretion.**—Cope determined the pregnanliol excreted in the urine of 100 pregnant women presenting various pregnancy disorders. The significant figure is not the concentration of pregnanliol but the total excretion in twenty-four hours. In the first few months of pregnancy, estimation of pregnanliol excretion can be of value in the diagnosis of pregnancy and its absence as evidence of a serious abnormality. Demonstration in a case of amenorrhea is strongly suggestive of pregnancy, for no other condition is so far known in which the two are associated. However, it must be certain that the pregnanliol excretion is not the normal prelude to an oncoming menstruation. To be of value, estimations must be capable of detecting as little as 3 mg. in the whole twenty-four hour output. Absence of pregnanliol from the urine of a woman with signs or symptoms of threatened abortion is evidence of abnormality, and the determination should be repeated. If persistently absent, either abortion is inevitable, the products of conception have been already partially or completely evacuated or the fetus has died without expulsion, missed abortion. Distinction between these possibilities must be made by clinical means. Treatment of threatened abortion with no pregnanliol excretion is not complete until it is certain that the uterine contents have been evacuated or definite evidence is obtained that the fetus is alive. The latter alternative occurs infrequently. As pregnanliol is believed to be derived from the placenta rather than the fetus, its excretion can be expected to continue when fragments of placental tissue are retained. In 1 of 6 cases of incomplete abortion with symptoms sufficient to require hospitalization, a doubtful trace of pregnanliol was found. Usually the retained fragments are either too small or too damaged to provide pregnanliol in recognizable amount. This may be influenced by the time elapsed since abortion. When intra-uterine death is suspected on clinical grounds absence of pregnanliol from the urine supports the diagnosis, but the

converse (as in incomplete abortion) is not always true. If fetal death is suspected and pregnanliol is found in the urine the estimation should be repeated at weekly intervals. A progressive fall is suggestive, and if the excretion falls to zero the evidence is almost conclusive. Pregnanliol excretion provides information comparable to that of the Aschheim-Zondek and Friedman tests. Chronic nephritis and toxemia of pregnancy may interfere with pregnanliol excretion. Deviations from the normal excretion in these conditions do not necessarily mean that the gestation is abnormal. Pregnanliol excretion seems assured of a place as a diagnostic aid in obstetric disorders, but further study is necessary for establishing its significance.

**Transfusion of Concentrated Suspensions of Erythrocytes for Anemia.**—Sixty-one patients with anemia were treated by MacQuaide and Mollison with an erythrocyte concentrate. The results suggest tentative conclusions as to the advantages of such therapy. Hypertonic saline solution was used as a diluent for the erythrocyte suspension because it produced less hemolysis than physiologic solution of sodium chloride. Hemolysis was further reduced by adding 8 per cent dextrose, insuring a concentration of dextrose of at least 1 per cent in the final mixture. Hypertonic saline solution is necessary presumably because the citrate saline into which the blood is originally taken is hypertonic and cells stored with this fluid become hypertonic to physiologic solution of sodium chloride. Very few reactions were encountered, suggesting that the leukocyte gel is responsible for the reactions following whole blood transfusions. In the preparation of the concentrated suspension, infection must be avoided. The cell suspension may be given (as soon as possible after preparation) through an ordinary administering apparatus. If the leukocyte gel is not removed, it is advisable to use a gas mantle or some other type of filter. The suspension was not warmed before administration. One bottle of the cell suspension, that is the cells of two bottles after plasma has been removed, usually raises the hemoglobin approximately 10 to 15 per cent. Thus, in one case, following a transfusion of six bottles of the cell concentrate the hemoglobin rose from 26 to 90 per cent and the erythrocytes from more than one million to more than five million per cubic millimeter. The use of the concentrated suspension is contraindicated in shock, in which the immediate need is to restore blood volume rather than to increase the number of erythrocytes. The incidence of rigors among the 61 cases was 6.5 per cent, in contrast to 22 per cent among 45 cases in which transfusions of whole stored blood were used.

**Journal of Laryngology and Otology, London**

55:361-404 (Aug.) 1940

Paranasal Approach to Intrasellar Tumors. F. R. Nager.—p. 361.

Bleeding from Tonsils Caused by Lack of Hormone. N. Viola.—p. 382.

Aspiration Through Tympanic Membrane. H. M. Jay.—p. 385.

**Lancet, London**

2:475-506 (Oct. 19) 1940

\*Adherent Pericardium: Constrictive and Nonconstrictive. T. G. Armstrong.—p. 475.

True Chylous Pleurisy: Report of Case. H. A. Cookson and D. A. Slade.—p. 477.

Blast from High Explosive: Preliminary Report on Ten Fatal Cases. G. Hadfield, R. H. A. Swain, Joan M. Ross, J. M. Drury-White and A. Jordan.—p. 478.

Alcohol Injection of Gasserian Ganglion for Migrainous Neuralgia. W. Harris.—p. 481.

Management of Cerebrospinal Fever Treated with Sulfapyridine. D. Williams and D. Brinton.—p. 482.

Sulfathiazole in Malaria. R. Pakenham-Walsh and A. T. Rennie.—p. 485.

Androgen and Pregnanliol Excretion in Hypertrichosis. R. Greene.—p. 486.

Influenza Virus and Incidence of Primary Lung Tumors in Mice. J. A. Campbell.—p. 487.

Bullet in Heart for Twenty-Three Years. G. G. Turner.—p. 487.

Bronzed Diabetes in a Woman. R. D. Lawrence.—p. 489.

**Adherent Pericardium.**—Armstrong calls attention to a diversity of opinion as regards the effects on the heart of an adherent pericardium. The following beliefs have been held: 1. That it may cause a cardiac failure characterized by a small heart associated with edema and ascites. 2. That it may have

no effect at all. 3. That it may cause failure with enlargement of the heart. In the light of modern knowledge the first two are undoubtedly correct, the third is unproved, and there is considerable evidence to show that it is untrue. An investigation was made into the histology of the pericardium in cases taken from the series of 114 necropsies at which complete adherence of the pericardium had been found; 4 cases of cardiac compression from which the pericardium had been removed at operation were added. The cases were divided into two groups: (1) adherent pericardium associated with chronic compression of the heart, the "constrictive" group, and (2) adherent pericardium without cardiac compression, the "nonconstrictive" group. It appeared that in constrictive pericarditis the compression of the heart depended on the type of fibrous tissue present, on its thickness, density and situation. The microscopic picture in the two groups showed that the density and toughness of the fibrous tissue is the deciding factor in producing cardiac compression. It also explains the success of pericardectomy. The removal of an adherent pericardium will lead to further adhesions in healing, but the peculiar fibrous tissue which compresses the heart does not repeat itself. When adhesions form, they have no effect on the heart. The different microscopic appearances in the two groups suggest also a difference in etiology and explain the widely held view that cardiac compression never follows a rheumatic pericarditis. On pathologic grounds as well as clinical, rheumatism can be excluded from the etiology of constrictive pericarditis. It has been known to be tuberculous and in some cases it has probably resulted from an unrecognized septic pericarditis. The author concludes that adherent pericardium may lead to cardiac failure associated with a small heart (constrictive type) or may have no effect on the heart at all (nonconstrictive type). There is no evidence that it causes enlargement of the heart unless it is accompanied by valvular or other cardiovascular disease.

### Medical Journal of Australia, Sydney

2:331-362 (Oct. 12) 1940

- Laryngeal Obstruction in Childhood. F. Arden.—p. 331.  
Microtomy of Eye. K. O'Day.—p. 336.  
Diagnosis of Malignant Disease. G. M. Oser.—p. 338.  
Treatment of Meningitis Due to Meningococcus, Haemophilus Influenzae, Pneumococcus and Streptococcus. D. G. Hamilton.—p. 342.

2:363-394 (Oct. 19) 1940

- \*Some Observations on Changes in Mineral Content of Plasma and Serum. B. Splatt.—p. 363.  
Effect of Testosterone Propionate on Pouch, Scrotum, Clitoris and Penis of Trichosurus Vulpecula. A. Bolliger and A. Carrodus.—p. 368.  
Relative Error in Examining Swabs for Corynebacterium Diphtheriae by Löffler Slope and by Clauberg Plate. H. Wilson.—p. 373.

### Changes in Mineral Content of Plasma and Serum.—

Splatt studied the changes in the plasma during the storage of blood and compared the serum obtained from individuals before and after hemorrhage and before and after transfusion with stored blood or serum. The alterations in the potassium, sodium, calcium, magnesium and chloride content of the plasma during the storage of blood show that a rapid rise in the potassium content of the plasma takes place as soon as the blood is placed in the anticoagulant solution. In citrate saline solution there was a 43 per cent increase of potassium at the end of seven hours, and at the end of twenty days the plasma contained 363 mg. of potassium per hundred cubic centimeters. In dextrose citrate solution the increase was 74 per cent at the end of seven hours and 305 per cent at the end of twenty days. In the sodium citrate and chloride solution of Manzells and Whitaker an increase of 71 per cent was obtained in seven hours, rising to 860 per cent at the end of the experiment. In their dextrin solution though the increase in seven hours was 10 per cent at the end of twenty days it was 520 per cent. The alteration in the potassium content of the plasma takes place long before in the onset of hemolysis. In all four solutions there was a fall in the sodium content of the plasma during storage; this was greatest with the citrate saline solution and least with the citrate chloride solution. The fall commenced as soon as the blood was mixed with the anticoagulant. The fall was independent of the onset of hemolysis. The changes in the calcium content of the plasma of the stored blood were irregular. In the blood preserved with the first three anticoagulants there was a steady

increase; in that preserved with the dextrin solution there was a preliminary fall followed by a rise at the end of thirteen days. Magnesium was estimated in the plasma of only 2 donors and the changes observed were also irregular. There was a fall in the chloride content of the plasma with all four preserving solutions. Hemolysis was slightly less in the blood preserved in the dextrose citrate and dextrin solutions. It appears that these two solutions have some advantage over the other solutions as there was only slight hemolysis at the end of thirteen days. The changes in the mineral content of the plasma justify the view that during storage the stroma of the erythrocytes ceases to be semipermeable and allows diffusion to take place between cells and plasma. Equilibrium is not usually reached before hemolysis occurs. The mineral content of serum was studied after loss of 1 pint (500 cc.) of blood by venipuncture in healthy subjects and hemorrhage occurring as a result of disease or accident. The serum of 23 normal adults after a fat-free breakfast was examined to establish values for comparison. The serum from these samples demonstrated no significant change in any of the mineral constituents. The average values for potassium, sodium, calcium and magnesium found in serum from 11 patients following severe hemorrhage and 1 patient after a moderate hemorrhage were similar to those of normal adults. Study of the mineral constituents of serum after the intravenous injection of stored blood (in 3 cases) and of stored serum (in 8 cases) showed no significant change in any of the constituents following stored blood transfusion. In none of the 8 given stored pooled serum was there any significant change in the potassium content of the serum, though obvious alterations in the level of sodium, calcium and chloride did occur. The 11 cases illustrate that in man serum or blood with a high potassium content, given at the rate of 500 cc. an hour, causes no ill effects or any significant change in the serum potassium level of the recipient. On the other hand, differences between the sodium and calcium in the transfused fluid and that in the recipient's blood before transfusion are sometimes reflected in a corresponding alteration in the amounts of these substances found in the recipient's serum after transfusion. The absence of toxic effects after the large doses of potassium in stored blood or serum is attributed to the presence of sufficient amounts of neutralizing sodium ions in them and to the slow rate of transfusion.

### Practitioner, London

145:213-308 (Oct.) 1940

- Medicine. H. Moore.—p. 213.  
Surgery. R. Kelly.—p. 221.  
Midwifery and Gynecology. A. Bourne.—p. 231.  
Tropical Diseases. P. H. Manson-Bahr.—p. 238.  
Diseases of Children. A. Moncrieff.—p. 244.  
Allergy. G. W. Bray.—p. 249.  
Diseases of Skin. P. B. Mumford.—p. 258.  
Venereal Disease. R. C. L. Batchelor.—p. 263.  
Psychologic Medicine. T. M. Ling.—p. 269.  
Recent Advances in Anesthesia. R. R. Macintosh.—p. 275.  
War Injuries of Eye and the General Practitioner. H. M. Traquair.—p. 282.  
Some Physiologic Aspects of the Present War. H. Hartridge.—p. 289.  
Modern Therapeutics: XVI. Some Modern Disinfectants and Antiseptics. C. H. Browning.—p. 293.

145:309-372 (Nov.) 1940

- Tonsils and Adenoids. L. Barrington-Ward.—p. 309.  
Common Winter Disorders of Nose and Throat Among Services Under War Conditions. H. V. O'Shea.—p. 316.  
Epistaxis. H. V. Forster.—p. 325.  
Some Common Diseases of Larynx. F. C. Ormerod.—p. 330.  
Treatment of War Wounds. W. H. Ogilvie.—p. 337.  
Emergence of an Unsuspected War Neurosis. C. Berg.—p. 345.  
New Methods of Blood Examination. Janet M. Vaughan.—p. 349.  
Surgical Aspects of Peptic Ulceration. H. Dodd.—p. 355.  
Modern Therapeutics: XVII. Chologogues and Drugs Acting on Liver. C. Newman.—p. 361.

### South African Medical Journal, Cape Town

14:371-390 (Oct. 12) 1940

- Individuality of the Blood, with Some Observations on Its Medicolegal Significance. I. Gordon.—p. 371.  
Medicolegal Significance of Blood Grouping. L. P. Bosman and W. P. Mulligan.—p. 373.  
Poisoning by Arsenic in South Africa. P. R. v. d. R. Copeman and P. A. E. Kamerman.—p. 379.  
Hereditoconstitutional Research in Psychiatry. L. A. Hurst.—p. 384.

**Presse Médicale, Paris**

48:585-600 (June 11) 1940

Abortive Latent Tuberculosis and Tuberculous Reinfection. P. Ameuille, A. Saenz and G. Canetti.—p. 585.

\*Antidiphtheria Vaccination in the Army. F. Meersseman and M. Hulin.—p. 589.

Cullen's Sign: Case. C. Olivier.—p. 593.

Blood Group Determination: Beth-Vincent Test. P. Theil.—p. 594.

**Antidiphtheria Vaccination in Army.**—According to Meersseman and Hulin, the morbidity rate for diphtheria fell rapidly in army units after the law of 1936, tightening the provisions of the law of 1931 and making toxoid prophylaxis universally compulsory for the army, was applied. (The law of 1931 had been limited to Schick-positives stationed in localities known as endemic centers of diphtheria.) In the garrison of Briançon, with a complement of 2,500 men in an endemic geographic area, the application of the law of 1931 had reduced the disease incidence from 40 to 13, only to see a striking exacerbation during the three succeeding years (69, 89, 40). On the introduction of universal military vaccination, morbidity fell to 4 cases in 1937 and 2 in 1938. In the garrison of Grenoble, numbering 4,000 men, limited vaccination lowered a previously high incidence of 111 to 50, 16, 14 and 13 cases for the respective years. When the regulations of the law of 1936 were applied, the diphtheria rate fell at once to 4, 5 and 2 cases. In the garrison of Lyons with 10,000 men, a diphtheria incidence which was still high in 1932 (112 cases) descended to a level of 4 and 3 cases in 1937 and 1938. The epidemiologic analysis for the fourteenth military region, totaling 32,000 men, which in 1932 still showed a diphtheria incidence of 319 cases, fell to 69, 25 and 18 cases, respectively, for the years 1936, 1937 and 1938, with no deaths. Similarly, a comparison of the diphtheria frequency for both the civilian (not subject to compulsory vaccination) and the military population of Lyons, which in 1932 showed a ratio of 410 against 112, in 1936, 1937 and 1938 exhibited the contrast of 410 to 7, 465 to 4 and 276 to 3. According to the authors the cumulatively favorable evidence for compulsory antidiphtheria vaccination was not weakened by such secondary renal and hepatic sequels as appeared. These were for the most part temporary and mild. Failure to attain a perfect score in diphtheria eradication is attributed to incomplete or interrupted vaccination, exemptions allowed and so on. In cases in which the disease appeared in spite of correct and complete vaccination, estimated at from 0.3 to 0.5 per cent of all army vaccinations, the authors observed many atypical and mild forms that frequently failed to react positively to the Schick test. Antidiphtheria therapy in the surveys here reported was associated almost from the beginning with typhoparatyphoid inoculation and since 1936 has been combined with antitetanus antitoxin. The statistical data cover the years 1926 to 1938.

**Annales Pédiatriques, Basel**

155:305-368 (Sept.) 1940

New Form of Acute Dementia in Childhood. J. König and I. Zimányi.—p. 305.

\*Therapeutic Experiences with Vitamin K. F. Hauser.—p. 325.

Want of Appetite in Childhood. J. Surányi.—p. 345.

**Vitamin K Therapy.**—Hauser reports favorable results obtained with vitamin K in hemorrhagic disease of the newborn. Vitamin K stimulated prothrombin action even in a case (age of child 4 days) terminating fatally in which, at necropsy, the gallbladder and bile ducts were found in a rudimentary stage of development. In another case (age of child 4 days) in which vitamin medication failed completely, necropsy disclosed a ruptured tentorium cerebelli. In a case of atresia of the bile duct, vitamin K made surgical intervention possible; in a case of stenosis of the bile ducts, the bile in the blood was seen to improve. Vitamin K was beneficial also in thrombasthenia associated with grave hemorrhagic diathesis. Coexistence of thrombopenia and hypocalcemia may have an adverse effect on the vitamin therapy and requires the cooperation of blood transfusions and calcium injections. Banked blood, however, is not suitable for transfusion in hemorrhagic diathesis, as it loses prothrombin rapidly. Microdetermination in the prothrombin count was made by a modification of the Quick-Kato-Fiechter method. In this the use of carefully decalcified mother's milk proved an

effective thrombokinase. Vitamin K administered in suitable daily doses for six days to 6 normal children demonstrated no effect on the fibrinogen content of the plasma.

**Schweizerische medizinische Wochenschrift, Basel**

70:925-944 (Sept. 28) 1940

\*Prophylaxis of Goiter in the Newborn. H. J. Wespi.—p. 925.

Experiences and Results in Traumatic Rupture of Urinary Bladder.

W. Brunner and H. Kübler.—p. 928.

Treatment of Dyspepsia in Nurslings with Dry Apple-Banana Powder.

Anna Botsztejn-Wyszevianska.—p. 932.

Diuretic Action of Prostagmine. W. Bachmann.—p. 935.

**Prophylaxis of Goiter in the Newborn.**—According to Wespi, iodine prophylaxis in the form of iodized salt was introduced in 1922 in a certain region in Switzerland where goiter was endemic and 50 per cent of the newborn had enlarged thyroids. This prophylactic measure greatly reduced the incidence of goiter in the newborn but did not bring about its complete disappearance. Eggenberger therefore introduced additional individual prophylaxis in pregnant women. They were given a stock mixture which increased the iodine content of the salt used in their household for from three to four times that of ordinary iodized salt. These measures resulted in the reduction of the incidence of struma in the newborn to 5.3 per cent. The iodine provided in iodized salt may not be adequate for pregnant women who are obliged to restrict their salt intake in order to avoid toxicosis. In such cases medication with potassium iodide can be resorted to. The author emphasizes that the reduction in the incidence of goiter is dependent on the quantity of iodine given in addition to that provided by the food. If during the last weeks of pregnancy the daily addition amounts to approximately 150 micrograms of potassium iodide, no measurable enlargement of the thyroid is evident in the nursing. If this quantity of iodine is administered during the last three months of pregnancy, enlargement of the thyroid is not even perceptible. The unequivocal results of the prophylaxis and the knowledge of the quantities of iodine ingested in regions where goiter is not endemic corroborate the correctness of the iodine deficiency theory of goiter. Since the present degree of iodization of cooking salt does not prevent the struma in the newborn in all cases, it should be increased so that each kilogram of salt contains at least 10 mg. of potassium iodide. This form of prophylaxis involves no danger since the small physiologic quantities of iodine do not cause existing strumas to become toxic.

**Archiv für Kinderheilkunde, Stuttgart**

120:49-112 (June 29) 1940

\*Prophylaxis of Rickets. K. Hofmeier.—p. 49.

Lactic Acid Bacterial Flora Occurring in Small Intestine of Nurslings.

W. Goeters.—p. 60.

Temporary Cardiac Murmurs in Nurslings. A. Meier.—p. 89.

Excretion Urography by Means of Subcutaneous Injection During Childhood. J. Siegl.—p. 94.

Otitis Media—An Initial Symptom of Pneumonia. H. W. Görges.—p. 100.

Action of Estrogen on Hemopoiesis. Maria Váradý.—p. 104.

**Prophylaxis of Rickets.**—According to Hofmeier the German organization for the protection of nurslings and young children, realizing the high incidence of rickets in Germany, particularly in some industrial regions, demanded a general prophylaxis, which is now being carried out. The health departments invite the mothers to bring their infants to a station where the nurslings are examined and the mothers are given a supply of irradiated ergosterol in oil with the instruction to give the nursing 5 drops of the oil daily. The first examination is made when the nurslings are in their third month of life. The supply of the irradiated ergosterol lasts about two months, at the end of which time the infants are reexamined and a new supply is furnished. At the end of this period the nurslings are examined for the third time. If at one of the examinations signs of rickets are detected, the nursing is referred to the family physician or to the insurance physician. In order to make certain that the prophylaxis is properly carried out, a nurse calls on the mother two or three weeks after the first supply of irradiated ergosterol has been given. Under unfavorable social conditions or when it is difficult to obtain cooperation from the mother, the prophylaxis can be carried out in the form of the so-called vitamin thrust, which consists in giving the nursing a single large dose (up to 15 mg. of vitamin

D<sub>2</sub>). This is sufficient to protect the infant for from four to six months. As a rule the prophylaxis is begun without consideration for the season of the year. In climatically favorable regions the treatment may be interrupted during the months of July and August. Early fruit and vegetable feeding and sufficient exposure to light and air are urged. In many children the prophylaxis of rickets has to be repeated during the second winter.

### Medizinische Welt, Berlin

14:341-368 (April 6) 1940

- \*Pathologic-Anatomic Effects of Poison Gases Employed in War. J. Wätjen.—p. 341.  
Lymphatic Reactions: C'en. G. Holler.—p. 344.  
Epilepsy in Children. E. Müller.—p. 348.  
Seminal Examinations and Sterile Marriages. W. Stemmer.—p. 351.  
Pseudocavities. P. Sibbel.—p. 354.

#### Effects of Phosgene and Dichloroethyl Sulfide.—

According to Wätjen, phosgene and dichloroethyl sulfide (mustard gas) have a distinctively different pathologic-anatomic toxicity. Phosgene, on inhalation, exerts a toxic effect within the area of the lungs by damaging the parenchyma of the lungs. It also modifies the blood picture. In concentrated doses it provokes acute asphyxia. In weaker concentrations it induces pulmonary edema associated with circulatory dysfunction. Distant extrapulmonary effects are not due to the absorptive power of phosgene but to the increased viscosity of the blood and the consequent retardation of the circulation. Patients who survive acute suffocation or pulmonary edemas may succumb to secondary infections, which produce localized pneumonia, chronic bronchitis and bronchiolitis obliterans, or they may suffer from bronchiectasis and emphysema years after the exposure. On the other hand, dichloroethyl sulfide is a treacherous gas in that it does not manifest its toxicity until after a latency of several hours. It affects particularly the upper respiratory passages, damages both exposed and protected skin surfaces by completely necrotizing exposed skin and mucous membrane surface and by attacking the blood vessels, especially the capillaries. Unlike phosgene, it is strongly absorptive, affects the entire metabolic system, induces blood degeneration and damages the hemopoietic organs, such as the bone marrow. Cases in which the gas is inhaled in vapor form present a particularly grave evolution. The upper respiratory passages undergo serious alterations that may lead to secondary lung changes and end fatally. At necropsy, pronounced hemosiderosis is observed in the spleen and liver.

### Monatschr. für Ohrenheilkunde, Berlin

74:155-200 (April) 1940

- Necrosis of Vocal Cord in Panmyelophthisis. F. Angyal.—p. 155.  
Epulis Laryngis: Case. E. Wessely.—p. 158.  
Grave Pharyngeal Phlegmon After Tonsillectomy in Local Anesthesia: Case. K. Koffler.—p. 162.  
\*Nasal Furuncles. F. J. Mayer.—p. 167.

**Nasal Furuncles.**—According to Mayer, conservative therapy, valuable in certain stages of nasal furuncles, should promptly yield to surgical intervention when bacterial invasion has spread from the nose to the inner orbital region and threatens to evolve into thrombosis of the cavernous sinus. A description of the operation, for which no originality is claimed, is given. Experience with 4 desperate delayed cases in which death was due to sinus thrombosis led the author to intervene surgically in 3 other cases with successful issue. His case material covers 91 patients, 64 of whom were men, treated during the course of ten years. The greatest incidence of nasal furuncles occurred during the third and fourth decades, with the seasonal trend highest during July and August. The ala nasi was affected thirty-four times, the tip of the nose twenty-nine and the nasal opening twenty-eight times. Among facial furuncles nasal furuncles, especially the ala nasi, are the most dangerous because of their medial position and the relation in anatomic structure between the nasal membrane and the cartilage. Complications ending fatally are due principally to generalized bacterial infection or to cavernous thrombosis. Hence prognosis is doubtful. Thrombosis in the cavernous sinus travels by way of the vena angularis and the vena ophthalmica to the sinus cavernosus, from which general infection as well as local invasion of the meninges

may occur. The author discusses the relative merits and suitability of conservative and surgical procedures. When tissue destruction and abscess formation have already set in, short wave therapy was found effective. In somewhat more advanced cases with no tissue destruction, alcohol applications or Burrow's solution were beneficial, especially when lips, cheek and eyelid were collaterally involved. Vitamin C was used only in cases of serious vitamin C impairment. Early diagnosis and prevention of complications controlled the author's therapeutic purpose.

### Acta Path. et Microbiol. Scandinavica, Copenhagen

17:255-376 (No. 3) 1940

- Serologic Analysis of High Molecular Crystallizable Protein in Myeloma Serum. T. Packalén.—p. 263.  
Immunity to Negatactic Substance of Bacteria. A. Pettersson.—p. 273.  
Relation of Hydrogen Ion Concentration to Disinfecting Power and Effect of Addition of Neutral Salts, with Special Consideration of Conditions in Physiologic Milieu. O. Ornstein.—p. 286.  
\*Rheumatic Fever Subsequent to Some Epidemics of Septic Sore Throat (Especially Milk Epidemics). T. Madsen and K. Kalbak.—p. 305.  
Pituitary Transplants in Rats. A. Westman and D. Jacobsohn.—p. 328.  
Dimensions of Villous Surface of Full Term Human Placenta: Relation to Permeability. A. K. Christoffersen.—p. 348.

**Rheumatic Fever.**—In view of the increasing tendency to associate rheumatic fever with sore throat produced by streptococci, Madsen and Kalbak review the experiences from some relatively well investigated angina epidemics in Denmark. Their study involves two fairly recent milk epidemics and the data obtained from several older epidemics found in reports from the Danish National Health Service. During the angina epidemic in Kolding of December 1926, about 2,500 of the inhabitants were attacked by a severe form of sore throat that in many cases assumed the form of phlegmonous angina. Notification was made by December 31 of 840 cases under medical treatment, including several with complications. The ascertained complications were 96 cases of phlegmon and abscess of the pharynx, 47 of otitis media, 33 of erysipelas of the face, 30 of rheumatic fever, 5 of laryngeal abscess and 2 of phlegmon of the tongue. The articular symptoms in the 30 patients with rheumatic fever made their appearance in from one to five weeks after the onset of sore throat, most often after a period during which the patients thought they were well, even though several of them still had some tiredness, lassitude and vague discomfort in various parts of the body. After such an interval they were taken suddenly ill with fever and joint pains, and gradually they had all the symptoms of typical rheumatic fever. The points to be emphasized are that the 30 patients were infected with hemolytic streptococci, that they previously had an attack of angina, that there was a symptom-free interval between the angina and the rheumatic fever and that only 3 of the 30 patients had a history of rheumatic fever. After the primary attack of rheumatic fever subsequent to the angina 9 patients suffered one relapse, 4 had two relapses and 1 had three relapses. The other recent milk epidemic occurred in greater Copenhagen during Aug. 10 to 28, 1935. It comprised about 10,000 cases. The overwhelming number of cases made it impracticable to investigate thoroughly the present question. Clinically the angina cases were quite in conformity with those of the 1926 epidemic. The disease was often accompanied by complications such as phlegmonous angina, otitis media, erysipelas, rheumatic fever, hemorrhagic nephritis and sepsis. As notification of rheumatic fever is compulsory, its frequency suddenly rose about three weeks after the great increase in angina in August. The independent reports of medical officers in various parts of the country show the very close connection between the angina epidemic and the increase of rheumatic fever following it. Discussion of some older angina epidemics shows subsequent increase in rheumatic fever. The description of these angina epidemics makes it rather probable that they have been of the same type as the two milk epidemics described, all starting off explosively and being markedly widespread within a definite, geographically well defined district. The morbidity percentage for rheumatic fever in these angina epidemics is about 3 per cent. In the majority of cases it is a primary attack. In all the examined cases streptococci were isolated from the tonsils. In the two recent milk epidemics the organisms identified were beta-hemolytic streptococci. It has not been possible to reexamine the patients to ascertain cardiac complications.

## Book Notices

**Hugh Young: A Surgeon's Autobiography.** Cloth. Price, \$5. Pp. 554, with over 100 drawings by William P. Didusch and 3 color prints. New York: Harcourt, Brace & Co., 1940.

**I Remember: The Autobiography of Abraham Flexner.** Cloth. Price, \$3.75. Pp. 414, with portraits. New York: Simon & Schuster, 1940.

**A Surgeon's Life: The Autobiography of J. M. T. Finney.** Cloth. Price, \$3.50. Pp. 396, with portrait. New York: G. P. Putnam's Sons, 1940.

**L. Emmett Holt: Pioneer of a Children's Century.** By R. L. Duffus and L. Emmett Holt Jr. Foreword by Edwards A. Park, M.D., Professor of Pediatrics, Johns Hopkins University, Baltimore. Cloth. Price, \$3. Pp. 295, with 19 illustrations. New York & London: D. Appleton-Century Company, Incorporated, 1940.

**The Life of Sir William Osler.** By Harvey Cushing. Complete in One Volume. Cloth. Price, \$5. Pp. 1,417, with 11 illustrations. New York, Toronto & London: Oxford University Press, 1940.

Among biographies and autobiographies, 1940 might well be characterized as Johns Hopkins year, with the great likelihood that the series will be climaxed by the new life of William H. Welch written by Dr. Simon Flexner.

The "Life of Sir William Osler," for which Harvey Cushing received the Pulitzer prize, is now made available in a one volume edition at a price representing about one half what a student would pay for an ordinary textbook. In a medical career, reading of the "Life of Sir William Osler" will certainly help the student as much as most available textbooks. This book is heartily recommended to every medical student and practicing physician. If the art of medical practice is not enhanced by reading this book, it will at least do much to aid the reader's literary style.

Of chief interest in the autobiography of Abraham Flexner, for medical readers, is the record of the manner in which Mr. Flexner was influenced by German medical education. This influence has had its repercussion on many an American medical school, including particularly Johns Hopkins University School of Medicine, Washington University School of Medicine, Vanderbilt University School of Medicine, Cornell and the University of Chicago. For Mr. Flexner German medical education, as it existed before the Nazis, has been the ideal. To him a full time faculty in both preclinical and clinical branches represents all that is superb. Among physicians generally there has been some doubt as to some of the parts of this program. There is no agreement on the necessity for having all full time teachers in the clinical branches, particularly the specialties. Many physicians feel that such a system is ideal for the training of teachers and investigators but that it fails to emphasize those aspects of medical practice chiefly concerned in the care of the sick.

Mr. Flexner has had, however, a career which extended his influence far beyond the field of medicine. His point of view has done much to determine other aspects of education and culture. He records his life from the time he first began to study in Louisville to the day when he departed from the Institute for Advanced Study in Princeton. In that period he had innumerable contacts with great philanthropists, and he studied such varied problems as general education and the spread of prostitution. His sense of humor saves many a stilted passage from being trite. Certainly one must enjoy with him his technic in the handling of men of great wealth who found themselves beyond their depth in matters of culture and education.

If there is any fault at all to find, it is in the didacticism which is the mark of the teacher. Nowhere in this book is there any indication that its author may occasionally have supported a wrong point of view. Nowhere is there any recognition of the possibility that progress may have been delayed by a too rigid insistence on the author's own principles.

Dr. Hugh Young writes colorfully of the life and development of medical practice of a great pioneer in the new specialty of urology. He was born in Texas, graduated from the University of Virginia, did postgraduate training in Johns Hopkins Hospital and became a citizen of the world. He has brought to all his work a vast enjoyment, and those who know Dr. Hugh Young will read his enjoyment in the writing of his autobiography in every page of this work. Primary among

its features is the story of the development and improvement of the cystoscope. The name of Dr. Young is associated with innumerable devices involved in genito-urinary surgery. The great names which are featured in the pages of this book include those of President Wilson, President Quezon of the Philippines, "Diamond" Jim Brady, Ambassador Bingham, General Pershing, Harvey Cushing, Jesse Jones and Governor Ritchie—names familiar to all in our generation. The influence of Dr. Hugh Young was largely responsible for the establishment of the Brady Institute, from which have come many notable discoveries.

Much of this book is concerned with the work of Dr. Young as head of the urologic and venereal disease services in the World War. These war experiences are replete with personalities and with humor—the latter of the type definitely related to Dr. Young's specialty.

A conspicuous and extraordinary feature of this volume is the surgical illustrations. Whether or not to include them was many times debated in the mind of Dr. Young and often discussed with his friends and advisers. Certainly for the average reader, even fairly well educated, they are somewhat too profuse and quite technical. Nevertheless, it was Mr. Mencken's advice that these pictures be included, since they are intimately a part of the life of the author and indeed the very mark of many of his scientific contributions.

Here is a book which will do much to enlighten many a young man in the story of medical practice in our times. Toward the end of the book come a number of chapters touching but lightly on many minor interests of Dr. Young, including his memberships in medical organizations, his travels abroad and his association with innumerable civic committees. The autobiography of Dr. Young is a record of a great medical citizen who has enjoyed his life and who quite evidently is delighted to tell about it.

For fifty years the name of Dr. J. M. T. Finney has been an inspiration to young men in medicine and particularly to those in surgery. He was born in Natchez, Mississippi, more than three quarters of a century ago. He received his bachelor's degree at Princeton in 1884 and his M.D. at Harvard Medical School in 1889. Finney was a member of the football teams of both universities, since colleges were not in those days limited to three years of service of an undergraduate. As one reads the life of Dr. Finney, one might be inclined to recommend to a young man, as one of the important factors for success, a place on the football team of his alma mater. Unquestionably it brought Dr. Finney many important contacts. However, there are too many football men whose careers end with that contribution to our civilization to accept the idea as a scientific one.

From Harvard University Dr. Finney went to the Massachusetts General Hospital, and from there he went to aid Halsted at the Johns Hopkins Hospital. The time was the beginning of the careers of Halsted, Osler, Kelly and Welch—a period as well reflected in Finney's autobiography as in many of the other books available.

The story tells of a Scotchman with a real Scotch sense of humor—and there is something quite distinctive about that. It includes a personal evaluation of many a great figure in medicine, and an evaluation well worth having. The beginning of clean surgery and the development of rubber gloves is carefully recorded with innumerable accounts of the details of a surgical practice. Occasionally come poems written by brilliant members of the Finney family. As one reads the autobiography of Dr. Finney, one becomes increasingly interested in the intimate anecdotes discussing affairs of the recent past. Not the least interesting is the chapter describing how Finney was sent home from France to tell President Wilson that General Pershing wanted Merritte Ireland as surgeon general following the retirement of Gorgas.

The section describing the illnesses of Mrs. Harding and of President Harding is most enlightening concerning the inability of many a person in high places to judge for himself in matters medical. One finds anecdotes of President Coolidge, of Dr. Thayer and of other names great in the history of medicine.

As this book draws to its close, several chapters reveal the philosophy of living that has given to Dr. Finney increasingly the respect of all of medicine. Here, for instance, is his view of the hospital:

To summarize, a hospital is primarily a place in which sick people are cared for. Their comfort and welfare should always take precedence over everything else. The less red tape in the way of hospital rules and regulations, the better. These latter are only for those who need them and should be kept in the background for use only as occasion requires. Courtesy, kindness, friendliness and consideration are qualities that add greatly to a hospital's effectiveness. Of course, the acid test of a hospital is in the character and results of the professional treatment received there. This in turn depends largely on the personnel of the professional staff, its training and ability. Much depends too on the character of the nursing. Unless these are up to the mark, little else matters, but granted they are what they should be, the other considerations add greatly to a hospital's efficiency and to the welfare, both physical and mental, of the patient, and be it remembered that without them the highest degree of efficiency is unattainable.

In what has just been said, I have been referring to hospitals in general. So-called teaching hospitals, that is those connected with medical schools, differ from others in that the patients are studied by medical students and used as subjects for clinical teaching by members of the visiting staff. The function of the teaching hospital is twofold: humanitarian and educational. These two functions are not antagonistic but rather complementary and, when properly conducted, work no hardship to the patient. Quite the contrary, it reacts to his advantage in that cases which are used for clinical demonstrations are as a rule worked up very thoroughly; more so, if possible, than with the general average of patients. Then too, in demonstrating them before the class the instructor exercises of necessity the greatest possible care in establishing a correct diagnosis and carrying out the line of treatment indicated.

That hospital in which the welfare of the patient from every angle is the prime consideration of every member of the staff, professional or lay, will never want for grateful patients who will continually sing its praises, in season and out, and not infrequently show their gratitude in a more material fashion.

Here too is an anecdote concerning the Henry Ford Hospital in Detroit, which was planned as an institution that would run without a deficit but which Mr. Ford later admitted had never yet broken even.

There are sections on the nurse and on fee splitting and on socialized medicine, and there is an encouraging statement which urges the American medical profession to support the ideals and objectives of the American Medical Association. Here Dr. Finney says:

Organized medicine is prepared to do everything in its power to provide adequate medical care for every one who needs the services of a physician. It stands to reason that the members of the medical profession, since this matter of the public health is their especial province, are the proper persons to bear the responsibility, and, so long as political interference in the form of governmental control can be kept out of the picture, they may safely be trusted to find a satisfactory solution.

Indeed, one cannot forbear to quote a final few sentences:

Elsewhere I have endeavored to define medicine as "a profession ennobled by men actuated solely by their desire to devote their time and their talents to the relief of suffering humanity, willing, yes glad, at any time, if need be, to lay down their own lives for those of their fellowmen; whose membership should embrace only men of singleness of purpose, unselfish, high minded, zealous in their efforts to wrest from Nature the keys to her many mysteries; men who, unconsciously perhaps, in character and conduct reflect in varying degree the life and spirit of 'The Great Physician'; a profession free from taint of commercialism or graft; in which there shall be no room for the base, the unscrupulous, the ignorant or the unskilled; in which the test for membership has to do only with character and attainment." Are our ideals too high? Are we striving after the unattainable? After over fifty years of close association with members of the profession, frankly I do not think so. Unquestionably, not all members of the medical profession measure up to these requirements. But doctors are only human, as a class perhaps more human than any similar group of individuals, because from the very character of their work they gain such insight into human nature and thus come to understand it so well and respect it so highly. This is one of the chief characteristics of the true doctor and one of the crowning glories of a profession most exacting in its demands upon the time and talents of its members, and at the same time offering unlimited opportunities for usefulness in the way of service to humanity. It is this human element, this call to the aid of his fellowmen, wherein lies the charm that appeals so strongly to the true physician. The joy and satisfaction experienced in relieving the ills and ministering to the wants of humanity more than compensate him for the loss of the larger social and pecuniary returns that come from other less onerous and responsible vocations. The true physician is supremely happy in his work. He could not be happy doing anything else. Once having caught the vision as it unfolds before his gaze, all else fades into insignificance.

Most recent is the biography of L. Emmett Holt, written by a distinguished writer, Mr. R. L. Duffus, and by Dr. L. Emmett Holt Jr. For some time it has been thought that after the Bible the next best seller of all time has been "The Care and Feeding of Children," written by Dr. L. Emmett Holt.

This book traces the life of Holt from his boyhood in a small town in New York State to his death following his retirement as professor of the diseases of children at Johns Hopkins University. It is a bright but not a distinguished picture, since it partakes a little too much of the diary and chronological record. Here, however, is the story of the beginning of the *Archives of Pediatrics* and of the *American Journal of Diseases of Children*. Here is an account of the coming of antitoxin to aid the physician in his attack on diphtheria and of the crucial years which saw the development of hospitals for children. Here is the story of the production of "Diseases of Infancy and Childhood" as a fundamental textbook in pediatric practice. In his work Dr. Holt traveled throughout the United States and many foreign countries, and the concluding chapters of the book are largely devoted to letters sent home from many of these trips.

This book will be of great interest, therefore, particularly to pediatricians. It somehow lacks the depth and philosophy of Finney's autobiography, the dynamism and enjoyment of the life of Hugh Young. No doubt the comparison is invidious. Yet at the time when the records of the lives of the men of Hopkins have come in such multiple quantities, it is a comparison which must inevitably be made. Knowing the great contribution of Dr. Holt, one feels perhaps that his biographers were somewhat too close to their subject to realize that his fundamental contribution was the projection of vast knowledge of benefit to the public in such a form as to make it available to all mankind. For that pioneer contribution, if for no other, his name deserves enduring fame. One would have welcomed a long chapter indicating clearly the story of the reception of this effort by the medical profession and the manner in which it ultimately won acclaim.

In these five books is the history of an epoch. They constitute valuable source material for every student of the history of medicine. They represent many hours of enjoyable reading and many a moment of inspiration for every student of medical science.

**Vitamin Therapy in General Practice.** By Edgar S. Gordon, M.D., M.A., Associate in Medicine and Instructor in Physiological Chemistry, University of Wisconsin, Madison, and Elmer L. Serrinhaus, M.D., F.A.C.P., Professor of Medicine, University of Wisconsin, Madison. Cloth. Price, \$2.75. Pp. 258, with 35 illustrations. Chicago: Year Book Publishers, Inc., 1940.

This little volume is an excellent guide to the intelligent and rational use of vitamins in general practice. Particularly is the first chapter recommended to every one who prescribes vitamins. Each of the next ten chapters is devoted to one substance. The text is conservatively selected and clearly presented. The majority of the illustrations exhibit the pathology of clinical deficiencies. The last eight chapters deal with nutritional requirements other than vitamins. At times this material appears oversimplified. Even the general practitioner is accustomed to reading and interpreting highly technical material and hence it appears unnecessary to write for him textual material that sacrifices factual information for simplicity. However, the information is sound and reliable. The style is smooth and the composition is lucid. The appendix contains a variety of data that may be of value. The bibliography is limited to seven textbooks and monographs published within the past two years, each covering a special phase of the subject.

**Comparative Psychology: A Comprehensive Treatise.** By Carl J. Warden, Ph.D., Associate Professor of Psychology, Columbia University, New York, Thomas N. Jenkins, Ph.D., Associate Professor of Psychology, New York University, and Lucien H. Warner, Ph.D., Oplon Research Corporation, New York City. Volume II: Plants and Invertebrates. Psychology Series. Albert T. Poffenberger, Ph.D., Editor, Professor of Psychology, Columbia University. Cloth. Price, \$6. Pp. 1,070, with 168 illustrations. New York: Ronald Press Company, 1940.

Volumes I and III of this comprehensive treatise on comparative psychology have already been reviewed in *THE JOURNAL*. The present book, in contradistinction to the first volume, treating of general principles, and the third, covering the concepts of vertebrate psychology, deals with plants and invertebrates. Those who are not fully conversant with recent advances in comparative psychology may look askance at the concept of plants having mental processes and also, for that matter, invertebrates having mental processes which can be considered in psychological terms. The plants are covered only in slight detail,



being, as a rule, nonmotile; they cannot exhibit behavior, and it is behavior on which psychologic processes of the lower living organisms is based. Bacteria, however, do behave in response to certain stimuli in a consistent fashion, and this might be called the psychology of the unicellular organisms. The remainder of the chapters in the present volume deal with the complete ascending cycle of the invertebrate from the unicellular organisms to the arthropods. It would amaze the reader not familiar with modern comparative psychology to see the comprehensive research which has been done on this subject: the reaction of the various animals to light stimuli, to sound, to sex, to motivation, and the ability to repeat certain processes which in higher animals is known as memory. All indicate elementary mental mechanisms. There is a comprehensive bibliography in this book, giving all the titles which have a bearing on the subject. In fact, a fifth of the pages of this thick monograph are used for the bibliography. The volume is too technical for the physician. It is, of course, of interest to the zoologist and the psychologist.

**Introduction to Medical Biometry and Statistics.** By Raymond Pearl, Professor of Biology in the School of Hygiene and Public Health, and in the Medical School, the Johns Hopkins University, Baltimore. Third edition. Cloth. Price, \$7. Pp. 537, with 121 illustrations. Philadelphia and London: W. B. Saunders Company, 1940.

The previous edition of this well known text and reference book appeared in 1931, so that, as the author himself states, the present revision is considerably overdue. In the interim a number of other excellent textbooks on the handling of medical statistics and laboratory data have appeared. Among these Pearl's treatment of the subject is definitely unique. Chapter 2, on some landmarks in the history of biostatistics, is interesting and is not duplicated in any other introductory volume. The emphasis in this book lies in the field of vital statistics and there is little discussion of the statistical management of clinical data. A portion of the book can be read without any extensive knowledge of higher mathematics but its use as a textbook in connection with a formal university or medical course would be more feasible for most than as the exclusive prop of any self-training project.

**The Practice of Medicine.** By Jonathan Campbell Meakins, M.D., LL.D., Professor of Medicine and Director of the Department of Medicine, McGill University, Montreal. Third edition. Cloth. Price, \$10. Pp. 1,430, with 562 illustrations. St. Louis: C. V. Mosby Company, 1940.

Especially interesting in this new edition are the discussions of vitamin K, hypertension, new information concerning the liver, and a vast amount of information on chemotherapy. This edition does not represent a complete reprinting but is a revision. Already the type begins to show some effects of printing and, no doubt, the next revision will demand a resetting of the material. Incidentally, on some of the pages the addition of new material, as interspersed with the older material, has made a spotty appearance. This is noticeable particularly on pages 954, 939 and 1030 as well as on many other pages. It will, perhaps, aid the reader in determining which of the material is new. Dr. Meakins' book has found a place for itself among modern textbooks on the practice of medicine.

**Histopathology of the Peripheral and Central Nervous Systems.** By George B. Hassin, M.D., Professor of Neurology, University of Illinois College of Medicine, Chicago. Second edition. Cloth. Price, \$7.50. Pp. 554, with 502 illustrations. New York & London: Paul B. Hoeber, Inc., 1940.

This edition of Hassin's *Histopathology of the Nervous System* is larger and contains beautiful illustrations. It is one of the best textbooks in the field of neuropathology. This edition differs from the first by the addition of an introductory chapter on general basic features of normal and pathologic histology. In addition there is a chapter on diseases of the cerebellum and an outline of the changes found in electrocution. There are five parts consisting of general considerations, diseases of the peripheral nerves, diseases of the spinal cord, diseases of the brain and staining methods. Hassin does not differentiate between neuritis and neuropathy but describes the types found in various disease entities. The author's chapters on inflammatory and degenerative diseases are excellent. Many parts in the present volume have been revised. The part on staining is extremely

practical and makes an added reason for having this book in one's library or laboratory. The bibliography is large. The book is highly recommended to all neurologists, neurosurgeons, pathologists and those physicians interested in histopathology.

**Books for Tired Eyes: A List of Books in Large Print.** Compiled by Charlotte Matson and Dorothy Wurzberg. Third edition. Paper. Price, 65 cents. Pp. 80. Chicago: American Library Association, 1940.

Here is a valuable pamphlet with lists of books that are printed in 12, 14 and 18 point type which are recommended for readers of various ages and classifications. The volume should be especially useful for persons of advanced years. There is a section on juvenile books which should be especially interesting to teachers.

**Séro-diagnostic de la syphilis: Études comparatives de la sensibilité et de la spécificité de différentes réactions actuellement employées.** Par Th. M. Vogelsang, chef de service de séro-bactériologie, laboratoire anatomo-pathologique du Dr. F. G. Gade à Bergen, Norvège. Paper. Pp. 217, with 11 illustrations. Bergen: J. W. Eldes Boktrykkeri, 1940.

According to the author, the volume presents a comparative study of the sensitivity and specificity of different tests employed in the serum diagnosis of syphilis. After a brief introductory discussion of the phenomena of complement fixation and precipitation in syphilis, the technics of the several tests are considered, followed by comparative results obtained with these tests in the author's laboratory. Serologic studies reported during recent years by the American evaluation committee on serodiagnostic methods, in which the tests are carried out by the respective authors, are of greater value in establishing the dependability of the respective methods.

**National Research Council of Canada, Review of Activities for the Year Ended March, 1939.** Published under the authority of the Hon. W. D. Euler, Chairman of the Committee of the Privy Council on Scientific and Industrial Research. N. R. C. No. 871. Paper. Price, 75 cents. Pp. 175. Ottawa, 1939.

Here are summarized the investigations carried out by this body to the end of March 1939. The research covers a wide field. Practically all the work done in the field of medicine has been previously published in medical periodicals. The budget for 1939-1940 approximates \$53,000 and the projects already approved are in the field of medical radiology, tuberculosis and rheumatic diseases. Minor grants have been made for problems relating to cancer, heart disease, chemotherapy, hormones and vitamins. Especially interesting is the number of researches in the field of aviation from every point of view.

**Edinburgh Post-Graduate Lectures in Medicine. Volume I.** Published for the Honyman Gillespie Trust. Cloth. Price, 10s. 6d. Pp. 513, with illustrations. Edinburgh & London: Oliver & Boyd, 1940.

This is a collection of a series of lectures given at Edinburgh University under a grant by an Edinburgh philanthropist. These thirty-three lectures were originally published in the *Edinburgh Medical Journal*, and before publication each contributor had opportunity to revise his material and bring it up to date. The problem of postgraduate teaching is discussed by Edwin Bramwell, who urges the establishment in Edinburgh of a postgraduate school which will provide not only "refresher" work but also more advanced and specialized teaching. The thirty-three lectures cover almost every phase of modern medical interest. Every physician will find here material helpful to him in his daily work.

**Food Values of Portions Commonly Used.** First edition compiled by Anna dePlanter Bowes, M.A., Director, Nutrition Education, Philadelphia Child Health Society, Philadelphia, and Charles F. Church, M.D., M.S. Third edition revised by Senior Author. Paper. Price, \$1. Pp. 31. Philadelphia. The Author, 1940.

This pamphlet, first published in 1937, is here brought up to date. Vitamin values are now expressed in international units when possible. There are also discussions of the effects of cooking on food values, and a summary of dietary requirements at various ages has been added. There is also some bibliography. The elements of information in the field of nutrition are not elsewhere more authentically stated than in these tables. Particularly valuable is the expression of data in measurements of approximate servings.

## Queries and Minor Notes

THE ANSWERS HERE PUBLISHED HAVE BEEN PREPARED BY COMPETENT AUTHORITIES. THEY DO NOT, HOWEVER, REPRESENT THE OPINIONS OF ANY OFFICIAL BODIES UNLESS SPECIFICALLY STATED IN THE REPLY. ANONYMOUS COMMUNICATIONS AND QUERIES ON POSTAL CARDS WILL NOT BE NOTICED. EVERY LETTER MUST CONTAIN THE WRITER'S NAME AND ADDRESS, BUT THESE WILL BE OMITTED ON REQUEST.

### PAROXYSMAL AURICULAR FIBRILLATION

To the Editor:—A man aged 69 was found eight years ago to have a duodenal ulcer, for which he received the customary treatment. He simultaneously had periodic attacks of auricular fibrillation, which came on suddenly and, on his lying down in time, quit as suddenly as they appeared. With these occurred frequency of urination every twenty or thirty minutes, of large quantities of light colored urine. He remained on a strict diet for about four years, during which time he had the periodic attacks of auricular fibrillation. About this time he began eating anything that he wanted and after a time had a recurrence of the ulcer symptoms. He then went on a strict diet for a year since which time he has had no trouble along that line, merely avoiding fried foods. The periodic attacks of fibrillation have continued. Early in the progress of this condition he was digitalized and given  $\frac{3}{4}$  of a grain of phenobarbital three times a day and finally it was discovered that the only medication that would stop the fibrillation was nembutal given in large doses, 3 to 6 grains, which put him to sleep and on awakening the fibrillation had ceased. Large doses of quinidine had no effect whatsoever. He has had no dyspnea with the attacks or at any other time. The heart is not enlarged, there are no murmurs and no arrhythmia, except an occasional extra systole. The first electrocardiograph showed no abnormality except one extra systole. A later electrocardiograph showed a slight auriculo-ventricular block, perhaps due to the digitalis. An electrocardiogram taken during the attack showed only fibrillation. He has never used liquor to excess and quit smoking 8 years ago. The blood pressure varies from 140 to 160 systolic and 80 to 90 diastolic. He is an active man and looks younger than his years. He is decidedly uncomfortable in high temperatures and sweats profusely. Physical examination showed nothing abnormal. Wassermann and Kahn tests were negative and the basal metabolism was within normal limits. I would like your opinion as to the probable cause of these attacks and suggestions as to therapy.

M.D., Montana

ANSWER.—The occurrence of paroxysmal auricular fibrillation in elderly persons is common and attributable to any one of many different exciting factors, only one of which is heart disease itself, although it is probably true that the combination of certain abnormalities of the heart and exciting factors especially favors its occurrence. There is no common association between duodenal ulcer and its treatment and paroxysmal auricular fibrillation.

A frequent symptom associated with paroxysmal tachycardia of any sort is frequency of urination and increase in amount of urine with low specific gravity.

The prognosis of paroxysmal auricular fibrillation is generally good as to life in the absence of evidence of important heart disease but uncertain as to persistent recurrence of the attacks.

The treatment is often difficult. Quinidine acts more favorably as a rule than other drugs, both from the standpoint of prevention and of treatment. It may be that in this particular patient, quinidine sulfate given in daily rations of three grains, 3, 4 or 5 times in twenty-four hours, over periods of months, might help to reduce the number and duration of the attacks. Even that it was ineffective on one or two occasions does not mean that it would not have some value over a long period of time. Digitalis is the drug of choice after quinidine and if quinidine is ineffective. It has two values; in the first place, under digitalis the heart rate tends to be less rapid during the paroxysms of fibrillation, and in the second place, the digitalis effect tends to establish permanent fibrillation with a reasonably slow ventricular rate which is a much more comfortable state than that of paroxysmal fibrillation when the paroxysms occur frequently.

### POSTCONCUSSION SYNDROME

To the Editor:—1. What is the effect on a patient suffering from a post-concussion syndrome of (a) heat over 90 F. and of (b) overactivity? 2. What is the mechanism? 3. Please give references. 4. What is the treatment of postconcussion syndrome, including the advisability of resuming work?

M.D., Massachusetts.

ANSWER.—The diagnosis of postconcussion syndrome should be limited to a condition arising from the result of brain injury in which there is a transient loss of, or a defect in, consciousness. There is no recognizable pathologic change in the brain substance, as this is a temporary state and the patient makes a

rapid and complete recovery. There is no chronic postconcussional state. Frequently the term postconcussional is used when postcontusional is really meant.

1. (a) Heat over 90 F., depending on the maximum temperature reached, should give increased headache, dizziness, emotional instability, irritability, mental confusion, increased pulse rate and perhaps an elevation of body temperature. The symptoms would depend on the age of the patient and on the severity of the condition. (b) Overactivity will act similarly to heat, of course depending on the severity of the symptoms. There may be an increased headache, inability to concentrate, increased loss of sleep and libido, intolerance to noise, easy fatigue, increased irritability with a tendency to avoid friends, and a decreased tolerance for alcohol.

2. Little is known of the pathology, as patients who present opportunity for clinical study recover rapidly and no postmortem examination is possible. If they die it is usually right after the accident and the time is insufficient to study symptoms. Trotter suggests that concussion is the result of momentary cerebral anemia from the compression or indentation of the skull. Others suggest that it may be a transitory cerebral edema.

3. "Injuries of the Skull, Brain and Spinal Cord," edited by Samuel Brock (Baltimore, Williams & Wilkins Company, 1940) has a chapter on concussion and contusion of the brain.

4. Treatment indicated is rest, both mental and physical, with mild sedation. A spinal puncture is indicated and, if the pressure is high, dehydration should be instituted. As the patient recovers completely in a short time there is no reason why he should not return to work. Special care should be taken to avoid a neurosis.

### SUBCUTANEOUS OXYGEN FOR ASTHMA

To the Editor:—Please discuss the use of oxygen by subcutaneous injection for the treatment of asthma. Galen M. Hoyer, M.D., Fort Riley, Kan.

ANSWER.—The use of oxygen subcutaneously was introduced by Bayeux of Paris in 1922. A review of the literature yields no clinical summary of its use in the treatment of asthma. This mode of oxygen therapy was instituted primarily for the treatment of pneumonia. Simon and Kirk, who advocate its use for asthma merely mention it as one of a half dozen conditions wherein it may be indicated. In general, they state that all conditions wherein an anoxia and asphyxia are present call for oxygen aid. Since the lungs may be so congested that pulmonary exchange of air is seriously hampered, they point out that subcutaneous absorption of air may be life saving. They advocate from 400 to 1,200 cc. of oxygen subcutaneously in a twenty-four hour period. The presence of crepitation indicates that the oxygen injected is not yet completely absorbed. The amount of oxygen consumed subcutaneously is small as compared to the volume used by funnel, catheter, mask or chamber. To this the sponsors of subcutaneous oxygen therapy state that the difference between the body's oxygen demand and supply is small and the need can be adequately fulfilled by the slow absorption of the subcutaneous oxygen. There are no statistics to verify their claims. The amount of oxygen injected is not sufficient to alter materially the oxygen content of the blood. Almost no one with large experience in the treatment of severe asthma uses oxygen by injections. Helium with oxygen has been used by some.

#### References:

- Bayeux, R.: Subcutaneous Injection of Oxygen in Influenza, *Bull. Acad. de méd.*, Paris 87: 176 (Feb. 7) 1922.  
Simon, O. B.: Subcutaneous Oxygen Therapy, *Clin. Med. & Surg.* 40: 155 (March) 1933.  
Kirk, T. S.: Use of Subcutaneous Injections of Oxygen, *Brit. M. J.* 2: 195 (Aug. 4) 1928.

### WELTMAN SERUM COAGULATION REACTION

To the Editor:—What is the status of the Weltman reaction or test? Is it of any particular value; or can it add nothing to what clinical manifestations plus white blood count and differential and a determination of the sedimentation rate will reveal?

M.D., Territory of Hawaii.

ANSWER.—The Weltman serum coagulation reaction has, if one is to judge from the literature, been used extensively in continental Europe, in particular in Austria and Germany. Evidently the reaction has been studied and used to only a small extent in the United States.

Exponents of the test believe that it aids in differentiating exudative and necrotic processes and nephrosis on the one hand

and parenchymatous damage of the liver, fibrotic processes or hemolytic processes on the other. All have agreed that the test is nonspecific in the sense that it does not establish the diagnosis of any particular disease. Attempts have been made to use it in the differential diagnosis of intrahepatic and extrahepatic jaundice, but the evidence does not warrant the conclusion that it serves any particularly useful purpose in this regard.

It is said that the study of the coagulation band offers more information than a study of the sedimentation rate, since sedimentation rates usually are increased in a wider group of diseases than those which show alteration of the coagulation band. Counts of leukocytes and differential counts usually are not particularly diagnostic in the types of diseases for which the determination of the coagulation band has been recommended.

It is doubtful whether the time will ever come when a careful clinical history and examination can be replaced by any single laboratory test.

#### ASEPTIC PRECAUTIONS FOR VAGINAL EXAMINATION DURING LABOR

**To the Editor:**—It is routine at this hospital for the supervising nurses in the maternity division to do vaginal examinations on patients in labor. The progress is followed in this manner. I am a young physician still in training. Before coming here I had always been taught that vaginal examinations should be done only under the most aseptic conditions. When I make rectal examinations I can see the smiles around me. I have been told that the dangers of vaginal examinations are mostly theoretical and that when I am out for a time I will soon "wise up" and forget most of the medical school theory. Now my question is: Are vaginal examinations a dangerous procedure? Are they done commonly by men in practice?

M.D., Pennsylvania.

**ANSWER.**—Yes, a vaginal examination without strict aseptic precautions can carry with it real danger. The possibility of thus introducing infection naturally is greater in an environment abounding in infective bacteria. In her own home a woman is exposed only to the germs to which she has become more or less immune, and the most dangerous agent that comes into the birth room is the doctor. Therefore even here aseptic precautions cannot be neglected.

To obviate most of these perils, rectal examinations for both kinds of practice are advised, but even these must be practiced with due regard to the rules of aseptic operating, and of the physiology of the pelvic organs.

Most physicians in country practice use sterilized rubber gloves and aseptic and antiseptic precautions in their obstetric work. Naturally their methods need not be so cumbersome as in hospital practice, but the principles of clean technique are indispensable.

#### MÉNIERE'S DISEASE AND HISTAMINE

**To the Editor:**—A woman 30 years old and apparently in good health presents symptoms suggestive of Ménière's syndrome. She has had attacks of vertigo lasting for five to ten minutes for the last three years, which have been worse during the past three months. At the time of the attack she is too dizzy to walk. Excitement is often a precursor to an attack. She may have an attack every day or once a month. She never faints. She has an aura of the attack which consists of a "click" in the left ear, then vertigo and a feeling of pressure in the ear; then there is a "buzzing" in the ear and the attack is over. Has histamine proved of value in the treatment of this condition? What other treatment is recommended?

M.D., Minnesota.

**To the Editor:**—What value does histamine have in the treatment of Ménière's disease? If some chance of helping not fraught with too much danger exists, I would like to try it on a 58 year old man. Will you give dosage, technique and contraindications? I just noticed a newspaper account of it quoting Dr. Bayard T. Horton.

Odis A. Cook, M.D., Anadarko, Okla.

**ANSWER.**—The 30 year old patient gives a characteristic clinical picture of Ménière's syndrome. The treatment should aim to remove any etiologic factors, and this, in many cases, suffices. Focal infection, food allergy, suppurative otitis media or excessive fluid intake are the most frequent causes. If no etiologic factors can be found, symptomatic treatment must be resorted to. Furstenberg's salt free diet with fluid intake limited to less than 1,000 cc. a day with or without the administration of ammonium chloride, 45 grains (3 Gm.) three times a day is effective in many cases.

Histamine acid phosphate has been used intravenously, 1.9 mg. in 250 cc. of physiologic solution of sodium chloride being given slowly at the rate of one drop per second by intravenous drip taking one or two hours to give (Shelden, C. H., and Horton, B. T.: Treatment of Ménière's Disease with Histamine Administered Intravenously, *Proc. Staff Meet., Mayo Clin.* 15:17 [Jan. 10] 1940). This is not without risk because of the possibility of too rapid administration with acute histamine shock.

It is chiefly used during an acute attack, but since such attacks are in nearly all cases of short duration it is not usually necessary. The Furstenberg regimen is far safer and probably gives as satisfactory results.

#### PAROXYSMAL TACHYCARDIA AND ALLERGY

**To the Editor:**—A woman for the past seventeen years has been having attacks of paroxysmal tachycardia. These attacks began with the menopause and though she is more than 60 years old she still has them, more frequent lately than before. They appear irregularly, sometimes once a week or perhaps only once a month, while occasionally there is an interval of only three days. The attack never relieves itself nor does vagus stimulation seem to have any effect. No drug has any effect except a hypodermic injection of morphine. She vomits in about twenty minutes and the attack is over. I have noticed of late years that the attacks seem to follow the ingestion of fresh fruit, particularly citrus fruits. I wonder whether the cause of her tachycardia could be allergic. I have never heard or read that any one had considered this functional heart condition to be allergic and I hope that you can give me some information on the matter. Needless to say she has been advised not to eat foods that seem to bring on her "heart attacks" but apparently she can't resist temptation.

Edward E. Williams, M.D., Naugatuck, Conn.

**ANSWER.**—The suggestion that paroxysmal tachycardia may, in certain instances, be on an allergic basis has been made by Thomas and Post in this country and Laubry and Fournier in France in 1925, and more recently (1938) by Harkavy here. The evidence offered is not particularly striking, although in the two cases of paroxysmal tachycardia reported by Harkavy there was a definite tachycardia following the ingestion of foods to which the patient was particularly sensitive; in one case lamb and cauliflower being the worst offenders, in the other, shellfish and chocolate. However, there would seem to be some doubt as to whether the tachycardia was a true paroxysmal tachycardia in most of the attacks discussed. Hume in 1930 stated that he had not encountered any association between paroxysmal tachycardia and asthma and migraine, and this was reaffirmed by Campbell and Elliott in 1939. Any real proof of this mechanism is lacking, and it must be said that if allergy plays a part in the etiology of paroxysmal tachycardia it is probably a minor one, numerically speaking.

#### References:

- Thomas, W. A., and Post, W. E.: Paroxysmal Tachycardia in Migraine *THE JOURNAL*, Feb. 1, 1925, p. 569.  
Laubry, C., and Mussio Fournier, J. C.: *Bull. et mém. Soc. méd. d. hôp. de Paris* 49: 404 (March 13) 1925.  
Hume, W. E.: *Lancet* 2: 1055 (Nov. 15) 1930.  
Harkavy, Joseph: *J. Mount Sinai Hosp.* 5: 273 (Nov.-Dec.) 1938.

#### RESISTANT URETHRITIS

**To the Editor:**—A man aged 45 contracted gonorrhea four years ago. From his account it would seem that both the anterior and posterior urethras were involved. Treatment was inadequate and the discharge never wholly disappeared, turning from the original thick purulent material to thin watery exudate, which appeared from time to time during the past four years. More recently, however, this watery discharge has become more profuse and more persistent. There are no other accompanying urologic symptoms. He does complain of pain in the lumbar spine, both sacro-iliac joints and the joints of the hands. On examination a small drop of thin watery, grayish white material can be expressed manually from the urethra. The first voided specimen is cloudy with long white shreds, which fall to the bottom of the glass. These microscopically show one day nothing but epithelial cells; again they may be composed of pus cells; again they may show an admixture of the two cells. The second voided specimen for the most part is clear. The prostate is not enlarged nor are the vesicles, and the secretions are negative for pus. There are three firm strictures of the urethra running from the proximal end of the penile to the bulbous urethra. At first these would not admit more than a No. 14 bougie but now admit a No. 27 sound but no more. The remainder of the genitalia are normal. Smear and culture of the urethral pus reveal pneumococci. No other organisms have been discovered on three cultures. No typing has been done. Treatment has consisted of (a) Dilatation of the strictures to No. 27; they cannot be dilated further. (b) Anterior-posterior urethral irrigations with potassium permanganate 1:8,000-1:2,000 and oxymercure cyanide 1:1,000. (c) Urethral instillations of silver nitrate 0.5 per cent, mild protein silver 5 to 10 per cent, strong protein silver 0.25 to 1 per cent, prostatic and seminal vesicle massage, sulfanilamide, sulfapyridine and sulfathiazole in therapeutic doses as for acute gonorrhea, all to no avail. I have recently been trying a diazotized pyridine compound. Thus far no change in his discharge has been noted. Would you suggest therapy?

M.D., Massachusetts.

**ANSWER.**—Urethritis, coexisting with urethral strictures, may be due either to the gonococcus or to nonspecific organisms. Nonspecific urethritis is a frequent lesion with stricture.

The treatment already given this patient would seem to be quite adequate if not carried out at intervals frequent enough to produce a chemical urethritis. Periodic soundings, massages and local injections at bimonthly or monthly intervals might be tried. Attempts to increase the size of the sound should be used cautiously. If improvement has not taken place within a reasonable time, cysto-urethroscopy should be done to search for other lesions.

## STERILITY IN OPERATING ROOMS

**To the Editor:**—I will appreciate any information with regard to the length of time operating and delivery rooms may remain "set up" and still be considered sterile. I find that in one of our hospitals it is the practice to cover over instruments and drapes with a sheet and allow them to remain in this condition frequently for a period of more than twelve hours (without being resterilized) before being used. Kindly advise me if this is considered proper practice.

M.D., Virginia.

**ANSWER:**—In many hospitals the supply tables for the operations of the day are set up in the morning and covered with sterile sheets until they are ready for use. This practice is undoubtedly superior to leaving them exposed during several operations, as is sometimes done. Covered tables can be kept for many hours (provided due care is exercised in placing and removing the sterile covering) with less danger of contamination than they undergo during the process of being set up in a room with a number of occupants even if all occupants wear masks. The number of viable bacteria settling on an exposed table can be greatly reduced by the use of a suitable canopy, and it seems unlikely that an appreciable number of bacteria would gain access to a sterile supply table with a close fitting sterile cover during a twelve to fifteen hour period, particularly in an unoccupied closed room.

Ten petri dishes of blood agar exposed for from one and one-half to five hours on covered tables of sterile supplies showed an average of 10.7 colonies per dish when incubated, while four similar plates exposed under the same conditions for twenty-four hours revealed an average of only six colonies per plate.

It seems quite likely that any contamination of the sterile table occurs during the time it is being stacked rather than during the time it remains covered in an unoccupied room. The fewer colonies on the tables left covered for twenty-four hours is accounted for by the fact that they were set up for the purpose only of the culture and required less time of exposure than the other tables, which were stacked with a larger quantity of supplies for the routine operations of the day. Similar petri dishes exposed to sedimentation from the air during a routine operation may show from twenty to as many as 200 or more colonies of bacteria per hour of exposure, depending on a variety of local conditions.

If it seems desirable, either the supply table alone when exposed or the entire room can be protected continuously (from 80 to 99 per cent effective) by the use of the appropriate wavelength and intensity of ultraviolet radiation. If this is used, however, a suitable installation must be made and precautions taken to give adequate protection to the occupants of the room.

## TRICHOMONAS VAGINALIS AND AMENORRHEA

**To the Editor:**—Is the vaginal mucosa in patients with functional amenorrhea more prone to *Trichomonas* infection than in normally menstruating women? I have seen three patients with amenorrhea (three or four menses a year) afflicted with *Trichomonas vaginalis* who were greatly improved when subjected to injections of pregnant mare's serum, the discharge and burning diminishing in severity and the menses being normalized in two, for the past five months. My experience with *Streptococcus subacidus* filtrate and vaccine has not been satisfactory. What is the impression of other users?

M.D., Michigan.

**ANSWER:**—The vaginal mucosa in patients with functional amenorrhea is not more but apparently less prone to *Trichomonas* infection because such infections are most uncommon in young girls and rather infrequent in women past the menopause. The improvement in the cases mentioned may have been due to the fact that pregnant mare's serum stimulated ovulation, which in turn brought about an increase in the acidity of the vaginal mucosa. It is known that estrogenic therapy in gonorrheal vulvovaginitis in children is efficacious only when the acidity of the vaginal secretion is increased. Likewise an easy way to relieve women of *Trichomonas vaginalis* vaginitis is to insert acid douches or similar medication into the vagina. Of course, relief experienced by the inquirer's patients may have been coincidental or may have been brought about by supplementary treatment such as douches and increased cleanliness after the attention of the patients was directed to the infection.

Falls and Hibbert (*Am. J. Obst. & Gynec.* 36:219 [Aug.] 1938) reported excellent results in cases of *Trichomonas vaginalis* infection by using *Streptococcus subacidus* vaccine but Karnaky (quoted in the Year Book of Obstetrics and Gynecology, Chicago, Year Book Publishers, 1938, p. 421) failed to observe any benefits in 100 cases.

## APPARENT RECURRENT HERPES ZOSTER

**To the Editor:**—A woman aged 28 has had recurring herpes zoster over a period of three years. It first started with a classic thoracic localization apparently affecting the ganglions of the posterior nerve roots and appeared with a painful vesicular cutaneous eruption of segmental distribution limited to one side of the body. Symptomatic treatment was instituted: whole blood intramuscularly, solution of posterior pituitary and much local care. From six to ten weeks after the eruption similar lesions appeared. At this time the patient was seen by dermatologists and other colleagues with always the same impression of herpes zoster. Foci of infection were sought: teeth, tonsils, sinuses, gallbladder, pelvis and rectum. No intercurrent infection was noted. The serologic reaction was negative. There was no traumatic history or any type of medication and the patient was otherwise healthy. Finally the lesions became more subtle in distribution, involving the upper division of the fifth nerve and sometimes leaving eschars. The patient gave a history of allergy in her family although having no manifestations herself. Eosinophils were found on nasal smear. Other causes were ruled out for the polymorphonuclear cells. Following grass, pollen, dander, food and other tests, specific sensitivity was shown to inhalants. Desensitization was instituted. The herpes zoster has recurred only twice in one year when desensitization was withdrawn over two weeks. We are wondering whether there is such an entity as chronic herpes zoster? If so, has it ever been controlled by desensitization?

John B. McDonald, M.D., Hollywood, Calif.

**ANSWER:**—The appearance of herpetic lesions calls for a differential diagnosis, which at times is extremely difficult. Herpes simplex, herpes zoster, traumatic herpes and herpes on an arsenical basis may all appear alike. The literature shows a unanimity of opinion regarding the rarity of recurrence of herpes zoster. So seldom does it recur that such instances appear as individual case reports. One attack of herpes zoster generally creates an immunity. Herpes simplex on the other hand tends to recur indefinitely. Coca mentions that occasionally herpes zoster is associated with an asthmatic attack (Coca, A. F.; Walzer, Matthew, and Thommen, A. A.: *Asthma and Hay Fever*, Springfield, Ill., Charles C. Thomas, 1931). He also speaks of recurrent herpes labialis (simplex) as associated with allergy to such foods as chocolate and cocoa. Since herpes zoster so seldom recurs, and since there is no known etiologic factor other than a virus, no desensitization has been done. It may be a mere coincidence that, in this case of apparent herpes zoster, attacks are becoming less frequent since the institution of desensitization therapy.

## OTOGENIC DISCHARGE WITH B. PROTEUS

**To the Editor:**—I have tried almost all the ordinary antiseptics in an endeavor to dry up a persistent foul purulent discharge from an ear following a radical mastoidectomy. The cavity contains no exuberant granulations, it is covered with smooth epithelium except in two small areas and there is no rough bone palpable in these areas. The culture from the discharge contains only a member of the *Bacillus proteus* group. Any information which you can give me with regard to treatment of a local infection with *Bacillus proteus* will be appreciated.

M.D., Oklahoma.

**ANSWER:**—As the cavity described does not present evidence of carious bone, it must be assumed that the discharge comes from either the middle ear or the petrosa. The most likely place in the middle ear for the discharge to come from will be hypotympanic cells. The source of petrosal disease could be determined only by careful x-ray examination and exploratory operation undertaken to discover fistulas and diseased cell tracts.

Gerzog has written a complete article on "*Bacillus Proteus* in Orogenic Infections" with some suggestion as to treatment. He states that otogenous vaccines have been found useful by others, and he himself employed a stock bacteriophage.

## References:

- Gerzog, B. G.: *Bacillus Proteus* in Orogenic Infections, Secondary Mastoiditis, Thrombosis of the Lateral Sinus and Bacteremia, *Arch. Otolaryng.* 30: 275 (Aug.) 1939.  
Williams, H. L.: Chronic Suppurative Lesions of the Petrous Pyramid, *ibid.* 29: 345 (Feb.) 1939.

## RECURRING FRACTURES OF METATARSALS

**To the Editor:**—In "Fractures and Other Bone and Joint Injuries" by Watson-Jones, a book published by the Williams and Wilkins Company in 1940, I read on page 636 "Spontaneous fracture may be a recurrent disability and some cases have been recorded of as many as three fractures of the same bone occurring at intervals of several years." Could you give me any reference or other basis for this statement?

William A. Evans, Jr., M.D., Detroit.

**ANSWER:**—As the quotation is from the chapter wherein march fractures of the metatarsals are discussed in Watson-Jones's book, it is presumed that the inquirer refers to march fractures of the metatarsals. Recurring fractures of this type are certainly uncommon and no reference in the literature on this phase of the subject has been found. No doubt it could happen.

# The Journal of the American Medical Association

Published Under the Auspices of the Board of Trustees

VOL. 116, No. 3

COPYRIGHT, 1941, BY AMERICAN MEDICAL ASSOCIATION  
CHICAGO, ILLINOIS

JANUARY 18, 1941

## THE TREATMENT OF SEPTICEMIA

RESULTS BEFORE AND SINCE THE ADVENT  
OF SULFAMIDO COMPOUNDS

WALLACE E. HERRELL, M.D.

AND

ALEX E. BROWN, M.D.

ROCHESTER, MINN.

We feel that enough time has elapsed since the introduction of sulfamido compounds for some evidence to have accumulated as to the merits of these compounds in the treatment of septicemia. By septicemia is understood "a morbid condition which is due to the presence of pathogenic bacteria in the blood stream with the symptoms which are associated with this clinical syndrome."

In 1938 E. C. Rosenow Jr. with one of us<sup>1</sup> reviewed the cases of septicemia which had been encountered at the Mayo Clinic over a period of three years, 1934 through 1936. During that time none of the sulfamido compounds were being used by us in the treatment of septicemia. The review of 1938 offered a control group of results which can be compared with results from the use of sulfamido preparations. Accordingly, from 1937 to 1939 inclusive, when sulfamido compounds were available, we collected a group of cases comparable to those collected in the period of three years from 1934 to 1936 (table 1). The slightly larger number of cases in the later series parallels the contemporaneous greater number of registrations at the clinic.

### INCLUSIONS AND EXCLUSIONS

All cases of septicemia (positive blood culture) encountered in the period 1937 to 1939 inclusive numbered 265 (table 1). Of these, ninety-one were cases of subacute bacterial endocarditis. This is a larger number of cases of subacute bacterial endocarditis than would be expected, judging from the number of similar cases encountered in the previous period. The increase probably is explainable on the basis that during the latter three years more cases than before were referred for an attempt at chemotherapy. However, at present we cannot report a single case in which sulfamido therapy has brought about cure of subacute bacterial endocarditis. These cases represent a clinical entity differing distinctly from true septicemia. For this reason they were excluded from the study of septicemia published in 1938 and they will be excluded henceforward from the present consideration.

With the cases of subacute bacterial endocarditis excluded, we had left for consideration 174 cases of septicemia caused by a variety of micro-organisms. Of these cases we excluded nineteen, representing six micro-organisms, because the number of cases corresponding with each of the micro-organisms concerned was too small to permit significant conclusions as to the results of chemotherapy. For the same reason a comparable miscellaneous group of twenty-five cases had been excluded from the study published in 1938.

Thus there now remained for our study 155 cases. Before we take up these cases, however, we have a few comments to make on some of the nineteen excluded cases. In this excluded group appear eight cases of infection with micro-organisms of the genus *Bacteroides*, which still carries, in our hands, a mortality rate of 100 per cent. Two cases of septicemia due to *Klebsiella pneumoniae* are mentioned primarily because of their rarity; both patients died in spite of what might be considered adequate chemotherapy. In one case of rat-bite fever (Haverhill fever) *Streptobacillus moniliformis* was obtained from the blood stream; the patient recovered.

Turning again to the 155 cases remaining for study, it is seen (table 1) that they consisted of cases in which the infecting micro-organism was a hemolytic streptococcus, *Streptococcus mitior* (*Streptococcus viridans*), *Staphylococcus aureus*, *Diplococcus pneumoniae* (*pneumococcus*) or *Escherichia coli* (*colon bacillus*). These 155 cases we separated into two groups. In the first of these two groups we included those cases in which sulfamido drugs were employed. In the second group were included those cases in which sulfamido drugs, although available, were not employed. These cases of the second group were encountered in 1937 and early 1938, before the drugs had proved themselves to the satisfaction of all clinicians; if the cases had been encountered later in the period, it is safe to say that sulfamido therapy would have been applied. In the first group were 103 cases; in the second, fifty-two cases.

Thus, for comparison with our 103 cases in which sulfamido compounds were employed we had two control groups in which sulfamido drugs were not used. One of these control groups was derived from the report of 1938, which, as has been said, included cases encountered from 1934 to 1936 inclusive; the other was derived from our own series and therefore had the advantage, from the scientific point of view, of being concurrent with the cases in which sulfamido drugs were employed.

### GENERAL RESULTS

In table 2 is shown a comparison of the series in which treatment was employed, with the two control series, as well as an analysis according to the infecting organism. There is no need to record here in the text

From the Division of Medicine, the Mayo Clinic.  
Read before the joint meeting of the Section on Practice of Medicine and the Section on Pharmacology and Therapeutics at the Ninety-First Annual Session of the American Medical Association, New York, June 14, 1940.  
1. Rosenow, E. C., Jr., and Brown, A. E.: *Septicemia: A Review of Cases, 1934-1936 Inclusive*, Proc. Staff Meet., Mayo Clin. 13:89-93 (Feb. 9) 1938.

the quantities which, recorded in the table, so clearly show the comparatively favorable rate of recovery when sulfamido drugs were used. By recovery we mean that the blood cultures became negative and the patients were entirely without evidence of infection of the blood stream. It is conservative, we think, to estimate that this form of therapy for septicemia has almost doubled the rates of recovery.

TABLE 1.—Septicemia (Positive Blood Culture), Total Series of 469 Cases, 1934-1939

Organism Identified	1937-1939 Number	1934-1936 Number
Hemolytic streptococcus.....	46	61
Streptococcus mitior (not causing subacute endocarditis).....	14	2
Staphylococcus aureus.....	44	29
Diplococcus pneumoniae.....	23	20
Escherichia coli.....	28	7
.....	8	0
.....	3	4
.....	0	1
Klebsiella pneumoniae.....	2	0
Aerogenes.....	4	2
Proteus ammoniae.....	0	1
Bacillus influenzae.....	0	1
Pseudomonas.....	1	0
Streptobacillus moniliformis.....	1	0
Small gram-negative (unclassified).....	0	10
Total.....	174	144
Subacute bacterial endocarditis.....	91	60
Grand total.....	265	204

Examining the results on the basis of the different organisms, we find that the greatest evidence of improvement was in the cases of infection with hemolytic streptococci and Staphylococcus aureus. Patients suffering from infection with Escherichia coli were considerably benefited with treatment, although other substances, such as mandelic acid and related preparations, gave fairly good results prior to the advent of sulfamido therapy. There was no marked effect of the drug in improving an already rather high rate of recovery from infection with Streptococcus mitior (Streptococcus viridans). The results with Diplococcus pneumoniae indicate no improvement from use of sulfamido compounds and we can do nothing more in this small series than to report our experience. Here, however, results were quite different when sodium sulfapyridine for intravenous administration was introduced by Marshall and Long<sup>2</sup> in 1939. With regard to the fifteen cases of infection with Diplococcus pneumoniae in which treatment was by sulfamido drugs and only three patients recovered, it should be noted that in our cases of pneumococcic septicemia the infection was overwhelming and the patients often were seen late in the course of their illness or in its terminal stages. We do not, therefore, offer an example of what might be expected in the presence of pneumococcic septicemia of less severity or if treatment was possible early in the disease. We shall continue to use the preparations in these cases because there is every reason to believe that we may accomplish some good; we can only wait until we have a larger series before we can speak conclusively.

As has been said, sulfamido preparations were in use at the Mayo Clinic throughout the period of three years 1937 to 1939. However, in the first two of these years, methods of administration of the drugs, selection of the best drug to use under existing circumstances, dosages, the proper concentration in the blood stream and our organization for this form of therapy were in their

developmental period. Naturally, therefore, some of the patients had what we would call, at the moment, inadequate treatment; others, fairly satisfactory treatment, and the patients recently treated (1939) what we would call, at the moment, well controlled and adequate treatment. The consequent difference in results in the first two years of the period, as compared with results in the third and last year, are shown in table 3. When attention is directed to infection with hemolytic streptococci or Staphylococcus aureus, it is evident that results were at least 10 per cent better in 1939 than they were in the previous two years. The improved results in treatment of infection with Staphylococcus aureus are attributable to the advent of sulfapyridine, which is superior to sulfanilamide in the treatment of infections due to this organism. The other three micro-organisms named in the table were represented by small numbers of cases and this may account for the statistical results relative to these organisms. The over-all picture given by table 3 represents a 6 per cent improvement in results for 1939 as compared with the previous two years.

RESULTS IN THE LIGHT OF PARTICULAR FACTORS

*Age.*—Age previously has been reported to be of great prognostic importance in cases of septicemia caused by hemolytic streptococci as well as in cases attributable to staphylococci. Table 4 deals with the factor of age in hemolytic streptococcus septicemia. In this table results obtained in the present series, in which sulfamido drugs were used, are compared with results in the former series, in which sulfamido drugs were not employed. As age increased there was a rather marked decrease in the rate of recovery when sulfamido preparations were not available. That is, a person past the age of 50 years who became a victim of hemolytic streptococcus septicemia had only nine chances out of 100 to recover. In the present series, all ages considered, is seen more than a doubling of the recovery

TABLE 2.—Sulfamido Treatment for Septicemia: Comparison of Results in Cases With and Without Treatment

Organism	Sulfamido Drugs			No Sulfamido Drugs					
	1937-1939			1937-1939			1934-1936		
	Total	No.	Per Cent	Total	No.	Per Cent	Total	No.	Per Cent
Hemolytic streptococcus.....	38	25	65.8	8	1	12.5	61	18	29.5
Streptococcus mitior.....	9	7	77.8	5	4	80.0	2	1	50.0
Staphylococcus aureus.....	27	15	55.6	17	2	11.8	29	10	34.5
Diplococcus pneumoniae.....	15	3	20.0	8	3	37.5	20	6	30.0
Escherichia coli.....	14	11	78.6	14	9	64.3	7	4	57.1
Total.....	103	61	59.2	52	19	36.5	119	39	32.8

rate resulting from treatment with sulfamido compounds. However, among persons more than 50 years of age, on the basis of our experience, the recovery rate has been increased sixfold. This means that the greatest improvement occurred in those ages in which the mortality was previously highest.

A similar analysis of the cases in which septicemia was caused by Staphylococcus aureus was made. This showed also that the greatest amount of improvement in the recovery rate occurred among people of the older ages (more than 50 years); nevertheless, this improvement was not as marked as in cases of streptococci

2. Marshall, E. K., Jr., and Long, P. H.: The Intravenous Use of Sodium Sulfapyridine, J. A. M. A. 112: 1671-1675 (April 29) 1939.



septicemia. It should be added, however, that effective chemotherapeutic agents for treatment of *Staphylococcus aureus* infection have not been available very long.

*Number of Colonies Per Cubic Centimeter; Initial Blood Culture.*—Previous experience has taught that colony counts in septicemia are a rather reliable prognostic indicator, especially if the cultures reveal more

TABLE 3.—Sulfamido Therapy for Septicemia, Results of 1937-1938 Compared with Results of 1939

Organism	1939			1937-1938		
	Recovered			Recovered		
	Patients Treated	No.	Per Cent	Patients Treated	No.	Per Cent
Hemolytic streptococcus..	21	15	71.4	17	10	58.8
Streptococcus mitior.....	3	2	66.7	6	5	83.3
Staphylococcus aureus....	13	8	61.5	14	7	50.0
Diplococcus pneumoniae..	8	2	25.0	7	1	14.3
Escherichia coli.....	8	6	75.0	6	5	83.3
Total.....	53	33	62.3	50	28	56.0

than 100 colonies per cubic centimeter of blood. For example, Rosenow and Brown reported that, among patients who had streptococcal septicemia and whose blood yielded, on culture, more than 100 colonies per cubic centimeter, the mortality was 83 per cent. Of those who had staphylococcal septicemia and whose blood cultures yielded a similar number of colonies, 90 per cent died. In the group in which the colonies of staphylococci numbered from 10 to 25 per cubic centimeter, a 50 per cent mortality resulted. In our study of association of colony counts with rates of recovery, we grouped together the patients with hemolytic streptococcus and *Staphylococcus aureus* infection (table 5). This table shows that, when sulfamido compounds are used in treatment, colony counts lose much of their prognostic significance. Approximately a 60 per cent recovery rate was experienced irrespective of the colony count.

*Maximal Leukocyte Count.*—Another impression previously has been that if the leukocyte count is less than 10,000 per cubic millimeter of blood the prognosis is most grave. Rosenow and Brown, for example, quoted a mortality rate of 100 per cent in streptococcal septicemia and 75 per cent in staphylococcal septicemia if the maximal leukocyte count was 10,000. If the counts were between 10,000 and 30,000, the mortality rate in both groups of cases was reported to be approximately 60 to 65 per cent. From a similar analysis it appears that in cases in which sulfamido drugs have been used in treatment the prognostic significance of the leukocyte count is of questionable value. In fact, of patients whose maximal leukocyte count was 10,000 or less as many recovered as in the group of cases in which the counts were up to 20,000 per cubic millimeter; the percentages of recovery were 55.6 and 61.0 respectively. Likewise, in a group of seven cases in which the maximal leukocyte count was 30,000 or more per cubic millimeter of blood, two of seven patients (40 per cent) recovered. Another factor of significance in connection with the leukocyte count must not be overlooked, since depression of the leukocyte count to 10,000 or less is not at all an uncommon accompaniment of sulfamido therapy in association with either of these types of septicemia. For that reason we feel justified in declaring that the maximal leukocyte response is no longer of prognostic significance but,

rather, that it is an observation to be made only with reference to the possible effect of sulfamido therapy itself on the hemopoietic system.

*Adequate versus Inadequate Treatment.*—We believe at present that the most significant feature in recovery is the adequacy of treatment. Still, we do not feel it fair to build the results of therapy entirely around this point. The reasons are clear: First, we do not wish to go on record as having arrived at what might be called completely adequate therapy; second, a tendency might exist to include all patients who recovered in the adequately treated group regardless of how much or how long they received one of the sulfamido compounds. Adequacy of treatment, to be sure, is closely followed in importance by the factor of the time which elapses between the onset of infection and the beginning of therapy. Likewise recovery, regardless of adequate treatment, is also dependent on the factor of complications; these will be dealt with separately.

We mean by adequate treatment that a patient has received one or several of the sulfamido drugs in dosages which would produce concentrations in the blood stream which we feel are indicated for treatment of septicemia and that treatment has been continued over a period sufficient to account for the clinical response. Looking at table 6, it becomes apparent that the highest recovery rate occurred in the group in which treatment could be called adequate. The table shows that a patient adequately treated has seven chances out of ten of recovering as against seven chances out of ten of dying when he is inadequately treated. We feel that this point cannot be too greatly emphasized for the sake of that small group of patients who, for one reason or another, receive inadequate treatment or are treated by persons not experienced in the management of septicemia. The development of a focus directly connected with the circulating blood, and which was ineradicable, namely, thrombophlebitis with infection or an infected heart valve, in general accounts for those patients who did not survive infection with

TABLE 4.—Sulfamido Therapy in Hemolytic Streptococcus Septicemia: Age Factor in Treated and Untreated Cases

Age	Sulfamido Drugs 1937-1939			No Sulfamido Drugs 1934-1936		
	Recovered			Recovered		
	Total Patients	No.	Per Cent	Total Patients	No.	Per Cent
0 to 24.....	9	8	88.9	14	8	57.1
25 to 49.....	12	7	58.3	25	8	32.0
50 and up.....	17	10	58.8	22	2	9.1
Total.....	38	25	65.8	61	18	29.5

hemolytic streptococci. It is seen in table 6 that the rate of recovery from infection with *Staphylococcus aureus* was approximately as high as that relative to hemolytic streptococci; this appears to be a distinct advance in therapy. Among the patients who did not survive infection with *Staphylococcus aureus*, complications similar to those mentioned were encountered in addition to the not infrequent multiple peripheral abscesses which occur in this type of sepsis. *Streptococcus mitior* (*Streptococcus viridans*), exclusive of those cases in which it causes subacute bacterial endocarditis, in general responds well to treatment with

sulfapyridine or sulfanilamide, as do the infections caused by *Escherichia coli*. We previously have explained the low recovery rate in cases of septicemia from *Diplococcus pneumoniae*.

SELECTION OF THE DRUG AND METHOD  
OF ADMINISTRATION

We have used six compounds of proved clinical worth for the treatment of septicemia. These compounds are azosulfamide, sulfanilamide, sulfapyridine,

TABLE 5.—Sulfamido Therapy in Hemolytic *Streptococcus* and *Staphylococcus Aureus* Infections: Significance of the Colony Count (Initial Blood Culture)

Colonies per Cubic Centimeter	Total Patients	Recovered	
		Number	Per Cent
Less than 25.....	26	16	61.5
25 to 99.....	12	8	66.7
100 to 199.....	16	9	56.2
200 and more.....	11	7	63.6
Total.....	65	40	61.5

the sodium salt of sulfapyridine, sulfamethylthiazole, and the sodium salt of sulfamethylthiazole. The following factors govern the selection of one of these compounds as that most suited for the infection to be treated: (1) variability of absorption and acetylation of sulfapyridine, (2) increased toxicity of sulfapyridine as compared with sulfanilamide, (3) decreased toxicity with associated decreased therapeutic effectiveness of azosulfamide as compared with sulfanilamide, and (4) variation of therapeutic effect of individual compounds in the presence of different types of organisms. Because of these factors, sulfanilamide is the best drug for infections produced by the beta hemolytic streptococcus, *Neisseria gonorrhoeae*, *Escherichia coli*, *Neisseria intracellularis* (meningococcus) and *Clostridium welchii*. Sulfapyridine is the best drug for infections produced by *Diplococcus pneumoniae*, *Streptococcus mitior* (*Streptococcus viridans*), *Staphylococcus aureus* and *Klebsiella pneumoniae*. Sulfamethylthiazole appears to be as effective as sulfapyridine against *Diplococcus pneumoniae* and *Staphylococcus aureus* and has the added advantage of not producing evident irritation in the gastrointestinal, renal or hemopoietic systems.<sup>3</sup> However, its use at the moment is inadvisable because of one significant complication: namely, lower motor neuron involvement. This complication afflicted three of nearly 150 patients treated by us for various types of infections, including six patients with *Staphylococcus aureus* septicemia. Sulfapyridine, because of its effect on the foregoing micro-organisms, as well as on beta hemolytic streptococci, is also the preferable drug for use in cases of septicemia of unknown cause. We believe that azosulfamide is of value in treating septicemia produced by organisms that are affected by sulfanilamide if neither sulfanilamide nor sulfapyridine is well tolerated, and we have used azosulfamide effectively in such conditions. The sodium salt of sulfapyridine is of value if sulfapyridine alone will not produce desired concentrations of drug in the blood. The same is true of the sodium salt of sulfamethylthiazole.

3. Herrell, W. E., and Brown, A. E.: The Clinical Use of Sulfamethylthiazole in Infections Caused by *Staphylococcus Aureus*: Preliminary Report, Proc. Staff Meet., Mayo Clin. 14: 753-758 (Nov. 29) 1939.

In using these various drugs in case of septicemia, it is necessary to obtain high concentrations of free drug in the blood, and the best results will be obtained if treatment is started at the earliest possible moment and at a time when foci of infection and destruction of tissue are minimal. In other words, it is essential that the initial doses immediately establish the concentration of drug desired in the blood and that subsequent doses be directed to maintaining the concentrations so established. Our experience has shown that any lowering of these concentrations before recovery has taken place will definitely prolong the course of illness and jeopardize recovery.

In using sulfanilamide, sulfapyridine or derivatives of thiazole in septicemia, in general it is advisable to obtain a concentration of 12 to 16 mg. of drug in 100 cc. of blood. We believe, however, that septicemia caused by *Staphylococcus aureus* presents a somewhat distinct entity in which the result will be best if the concentration of drug is kept at 16 to 20 mg. per hundred cubic centimeters of blood. In using sulfanilamide, the desired concentration of drug in the blood usually can be obtained by giving orally an initial dose of from 50 to 80 grains (3.3 to 5.2 Gm.) to patients weighing upward from 100 pounds (45 Kg.). Subsequent doses of from 15 to 20 grains (1 to 1.3 Gm.) of sulfanilamide, given orally at intervals of four hours throughout each twenty-four hours, usually will serve to maintain the levels thus established. In using sulfapyridine orally, however, it is as a rule impossible to obtain the high concentrations of drug in the blood which are desired without giving the sodium salt of sulfapyridine intravenously. As a rule, the use of from 15 to 22½ grains (1 to 1.5 Gm.) of sulfapyridine given orally at intervals of four hours throughout each twenty-four hours will produce the maximal concentration of drug in the blood that can be obtained by oral use of sulfapyridine alone. If the patient is unable

TABLE 6.—Sulfamido Treatment for Septicemia, 1937-1939: Results of Adequate versus Inadequate Treatment

Organisms	Treatment					
	Adequate Recovered			Inadequate Recovered		
	Total Patients	No.	Per Cent	Total Patients	No.	Per Cent
Hemolytic streptococcus..	31	24	77.4	7	1	14.3
Streptococcus mitior.....	7	6	85.7	2	1	50.0
Staphylococcus aureus....	16	12	75.0	11	3	27.3
Diplococcus pneumoniae..	10	3	30.0	5	0	....
Escherichia coli.....	10	8	80.0	4	3	75.0
Total.....	74	53	71.6	29	8	27.6

to swallow, oral use of sulfapyridine may be facilitated by administering the drug suspended in milk or water through a Rehfuß tube. Our practice has been to give the sodium salt of sulfapyridine intravenously in 5 per cent solution in distilled water and, as originally suggested by Marshall and Long, we have calculated the dose on the basis of using 0.06 Gm. of drug per kilogram of body weight. It is necessary, because of the marked alkalinity of this solution (*pH* about 10.7) that it be given directly into the vein and that it be given at a rate not to exceed 5 cc. per minute. At times we have given larger quantities of sodium sulfapyridine intravenously than the foregoing calculation indicates but we never have given more than

5 Gm. as a single dose. The previously calculated dose, or some portion of it, may be repeated intravenously at intervals of from six to eight hours as necessary to maintain the concentration of drug desired in the blood. In some instances we have thus used the sodium salt of sulfapyridine from one to three times daily for as long as ten days when this procedure has been necessary in order to maintain the desired concentration of drug in the blood. Our experience has led us to believe that the intravenous use of sodium sulfapyridine should be considered primarily to supplement oral use of sulfapyridine when it is desired to elevate rapidly the concentration of sulfapyridine in the blood or when it is impossible to maintain this concentration by oral therapy alone. Because of this, oral administration of sulfapyridine always should be started when intravenous administration of sodium sulfapyridine is begun. In only rare instances have we used the latter drug alone.

In using azosulfamide in septicemia, it is obvious that determinations of the concentration of sulfanilamide in the blood give no accurate index of the effectiveness of treatment. Unfortunately there is no laboratory test by which one can determine whether satisfactory amounts of this drug are being given, and the only criterion is clinical response. We have given 120 grains (7.8 Gm.) daily of azosulfamide orally in divided doses in cases of septicemia and we also have supplemented this by subcutaneous or intramuscular administration of from 50 to 80 cc. daily of the 2.5 per cent solution of azosulfamide. We have used azosulfamide only if the patient was intolerant to sulfanilamide or sulfapyridine.

It is not our intention to leave the impression that we disregard other factors in the management of septicemia. Foci of infection always are surgically eliminated in our cases of septicemia when such foci can be attacked. The improvement in our results in the management of septicemia, however, cannot be attributable to surgical procedures, since such procedures differed in no way in our present series from those performed prior to the advent of sulfamido compounds.

General supportive measures, including repeated transfusions of small quantities of blood, also are employed in the management of septicemia, especially if anemia is present, but here again this is a factor in treatment which has not changed in the slightest in the past three years.

#### SUMMARY

Enough time has elapsed since the introduction of sulfamido compounds to justify a study of the merits of these compounds in the treatment of septicemia. After exclusion of certain cases we had left for study 155 cases of septicemia caused variously by a hemolytic streptococcus, *Streptococcus mitior*, *Staphylococcus aureus*, *Diplococcus pneumoniae* and *Escherichia coli*. Of these 155 cases we selected the 103 in which sulfamido drugs had been employed and we compared the results in these cases not only with those in the fifty-two cases of the 155 in which these drugs had not been employed but also with results in 119 similar cases encountered in 1934 to 1936 inclusive, when sulfamido drugs were not available.

It is conservative, we think, to estimate that the use of these drugs in cases of septicemia has almost doubled the recovery rates, in general, but this does not mean that results in the presence of different organisms are uniform. In any series of cases of septicemia, by far the larger proportion of the cases are caused by hemolytic streptococci and *Staphylococcus aureus*. Fortunately

these are the two micro-organisms against which, in our experience, sulfamido drugs have proved most effective.

Prior to the advent of sulfamido therapy, three factors were of great prognostic significance in septicemia. These were the age of the patient, the colony count on initial blood culture and the maximal leukocyte count. These factors, we found, were of reduced significance when sulfamido drugs were used. Evidence to support this statement from our series is that (1) among patients more than 50 years of age the recovery rate was increased sixfold, (2) approximately as many patients recovered, whether the initial colony count was low or high, and (3) the recovery rate was not substantially affected whether the maximal leukocyte count was below or above 10,000 per cubic millimeter of blood.

Our experience indicated that in the treatment of a series of cases of septicemia caused variously by the five micro-organisms named in a previous paragraph the single factor of greatest importance was adequacy of treatment. Evidence of this is that, when adequately treated with sulfamido compounds, patients had a seven out of ten chance of recovery as against a seven out of ten chance of dying if inadequately treated. In the latter group, results were no better than if sulfamido drugs had been completely withheld.

#### ABSTRACT OF DISCUSSION

DR. PERRIN H. LONG, Baltimore: It is a pleasure to talk with Dr. Herrell and Dr. Brown about their experience with sulfanilamide and its derivatives. We are generally in complete agreement. They have done a real service in collecting the data at their disposal. It is time for all of us to find out what actually has happened to people who have been given these compounds during the past four years. All physicians can remember spectacular cases of meningitis, septicemia and other grave illnesses in which prompt response has occurred, but we have forgotten that there have been some cases in which recovery ought to have occurred but didn't. It is time to check up on all of our clinical data to find out what we can do to improve the results we are getting. The authors stressed an important factor, and that is the adequacy of treatment. When one is confronted with a disease that responds to treatment with these drugs, one should make up one's mind to cure it, so that enough of the drug will be given for a long enough period of time, and the chances are that the patient will do very well. As the authors pointed out, we should not forget that there are auxiliary types of treatment. Dr. Lockwood stressed that on Tuesday morning. In no instance should we depend on these drugs to do something that the knife can do much better. We must realize that patients need vitamins, they need fluids most badly when they are getting thiazole or sulfapyridine, and they need every measure of supportive treatment that we can give them. In every instance try to use every auxiliary method of treatment, because then again the cure rate in the various types of infections will go to an even higher point than exists today.

DR. WALLACE E. HERRELL, Rochester, Minn.: I failed to point out that these results are sound on the basis of available evidence and that the results have been brought about entirely as a result of sulfamido compounds. We of course attack any surgical lesion associated with the septicemia and we use all the supportive measures we used before, such as repeated transfusions. The important thing is that these measures have not changed since these compounds have been introduced, and for that reason one must conclude that the increase in recovery rates has resulted from use of these compounds. One point in Dr. Yater's discussion, both Dr. Long and I feel, should be stressed; namely, if these compounds are given early in any infection, however insignificant it may seem at the time, I am sure there will be less septicemia, and septicemia kills several thousand people a year in America.

## THE MEDICAL MANAGEMENT OF FRACTURES

CHARLES F. NELSON, M.D.

AND

ROLAND C. NELSON, M.D.

BEVERLY HILLS, CALIF.

The subject of delayed union and nonunion of fractures is still in a state of confusion. The orthopedic surgeon has made great strides in his department of the practice of medicine, but this progress is limited largely to the mechanical aspects of orthopedics. He has not scientifically explained the causes of delayed union or nonunion of fractures or of bone disease, especially arthritis.

The literature on factors concerned in metabolism of bone is confusing and is to a great extent confined to the study of individual elements without due regard to the relationship of all the physicochemical processes involved and their clinical interpretation and application to growth and regeneration of bone.

Some suggestions as to the medical management of fractures, based on a large number of clinical cases as well as on considerable experimental evidence, should be of interest at this time. The suggestions offered

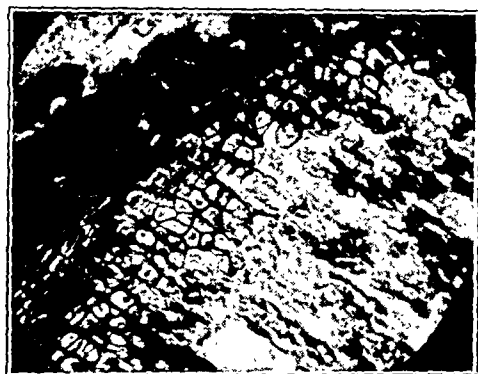


Fig. 1.—Section through the proximal end of a tibia of a normal rat (81 days old). Note the healthy appearance and regular arrangement of the cartilage cells at the zone of calcification. There is normal ossification.

here are based first on the study and management of approximately 1,000 fresh fractures treated in our clinic in the last five years without a failure in union; second, on the forced regeneration (by medical management) in several cases of fracture with greatly delayed unions, cases of osteoporosis, Paget's disease, fragilitas ossium and the like and, third, on animal experimentation.

Contrary to the generally accepted opinion as to the causes of nonunion of fractures, anything affecting the general physiology of the patient, such as endocrine imbalance, vitamin insufficiency and disturbed blood chemistry (especially the electrolytes), is potentially a causative factor in delayed union or nonunion of bone.

While it is granted that most fractures heal eventually, the medical management suggested in this paper, if properly applied, will produce rapid union in almost every case with a minimum amount of callus. This is of vast importance in the healing of fractures involving joints. Rapid union means bony union or "healing by first intention" and is not accompanied by excessive callus. Callus is osteoid tissue, and the ossification of it, or development of trabeculae in it, is a secondary process resulting in delayed union.

## THE SPECIFIC FACTORS GOVERNING BONE METABOLISM

1. Calcium and phosphorus concentrations of the serum.
2. The calcium-phosphorus ratio of the serum.
3. Activity of the parathyroid gland.
4. Vitamin D levels.

In order to appreciate the vital importance of these factors and to learn to control them, one should have a

clear concept of the effect of various deficiencies on osseous growth and maintenance. To assist in that direction we prepared an exhibit which was shown at the annual meeting of the American Medical Association in New York last June. This exhibit consisted of transparencies showing results obtained by selective medical management of recent fractures and of fractures with delayed union. Also there were models and prints of bones developed experimentally which showed the gross and microscopic effects of mineral deficiencies and the administration of vitamin D and solution of parathyroid on bone growth and maintenance.



Fig. 2.—Section through a femur of a rat (81 days old) fed on a low phosphorus (ricketic) diet. Note the persistence of embryonal cartilage along the articular surface. The cartilage cells at the zone of calcification are unhealthy and widely separated. The bone trabeculae are separated by considerable fibrocartilage.

## BLOOD CHEMISTRY

The availability of calcium and phosphorus for precipitation of bone depends partially on optimal concentration levels in the serum and on the ratio of calcium and phosphorus. Therefore, blood chemistry determinations of calcium and phosphorus levels in the serum should be made early in each case in order that accurate medical management may be instituted at once.

Our experience in the control of calcium and phosphorus metabolism in the treatment of nervous states as well as of bone problems has led us to believe that optimal levels of serum calcium are from 10.5 to 12 mg. per hundred cubic centimeters and optimal levels of serum phosphorus are from 3.5 to 4 mg.



Fig. 3.—Section through a femur of a rat (81 days old) fed a diet relatively high in phosphorus and low in calcium. Note the almost complete absence of bone trabeculae and the marked osteoporosis. The marrow encroaches on the zone of calcification.

per hundred cubic centimeters with a ratio of 3 calcium to 1 phosphorus (3 to 1). Our clinical experience has led us to believe that average variations of calcium levels of from 9 to 11 mg. and phosphorus levels of from 3 to 6 mg. per hundred cubic centimeters are not optimal levels.

In acromegalic types of bone, or in cases of osteoporosis, we recommend developing a serum calcium concentration of 12 mg. per hundred cubic centimeters and a serum phosphorus concentration of 4 mg. per hundred cubic centimeters to assure early union.

Blood chemistry determinations in approximately 1,000 fresh fracture cases revealed that 85 per cent of these patients have a low serum calcium level (below 10 mg. per hundred cubic centimeters) and 25 per cent have a low serum phosphorus level (below 3.5 mg. per hundred cubic centimeters). If accurate laboratory facilities are not available, it is justifiable in all cases of fracture to institute the medical management recommended for cases of low serum calcium.

After extensive experimental and clinical study we are convinced that the statement so frequently made that the levels of serum calcium and serum phosphorus cannot be controlled by medication and diet is erroneous.

#### MODIFIED CLARK TECHNIC FOR CALCIUM DETERMINATION

2 cc. of serum (fresh).

2 cc. of distilled water.

1 cc. of ammonium oxalate, saturated solution.

Mix and let stand at least four hours.

Centrifuge for from five to ten minutes

Remove supernatant fluid carefully.

Drain on filter paper.

Add 5 cc. of 2 per cent ammonia water.

Wash by centrifuge at once.

Drain and add 5 cc. of tenth normal sulfuric acid and heat to 75 C. in a water bath. Then titrate with hundredth normal potassium permanganate to the first permanent pink. The number of cubic centimeters of permanganate used equals the number of milligrams of calcium in 100 cc. of serum.

Special precautions:

1. Serum should be separated from clot as soon as possible.
2. Be sure serum contains no red blood cells.
3. Permanganate must be made fresh. Be sure titration is hundredth normal.
4. All containers must be clean and dry.

#### BENEDICT TECHNIC FOR PHOSPHORUS DETERMINATION

Filtrate 2 cc. of serum, 4 cc. of distilled water and 4 cc. of trichloroacetic acid.

Shake and allow to stand ten minutes. Filter.

Unknown: 3 cc. of filtrate, 5 cc. of distilled water.

Standard: 3 cc. of standard solution (0.025 mg.) of phosphorus, 5 cc. of distilled water.

Add to both tubes 1 cc. of Benedict's hydroquinone bisulfate reagent and 1 cc. of Benedict's molybdic acid reagent.

Place both tubes, loosely stoppered, in a beaker of boiling water for ten minutes. Cool and read in colorimeter.

$$\frac{RS}{RU} \times 0.025 \times \frac{100}{0.6} = \text{mg. of phosphorus in 100 cc. of serum}$$

If necessary to mail blood to a laboratory, send 10 cc. of centrifuged blood serum immediately after it is drawn (patient fasting). Send it special delivery air mail (in refrigeration).

#### MEDICAL MANAGEMENT

**Low Calcium.**—Low serum calcium may result from impaired parathyroid function, insufficient calcium intake and absorption or too much phosphorus consumption or retention. In cases of low serum calcium concentration, give at least 1 quart (liter) of milk daily. Give 1 drachm (4 Gm.) of calcium gluconate powder

thoroughly dissolved in 4 or 5 ounces (from 120 to 150 cc.) of hot water one-half hour before meals daily. Do not substitute dicalcium phosphate for calcium. In cases of low serum calcium with a high serum phosphorus concentration it is important to withhold the foods with a high phosphorus content such as liver, fish, eggs, cheese, green vegetables and cereals for from ten to fourteen days until a proper ratio of calcium and phosphorus is established.

In the management of simple Colles' fracture, or fracture of small bones (except carpals and tarsals), if the roentgenograms indicate fairly good bone texture it is not necessary to give calcium intravenously unless the serum calcium level is below 10 mg. per hundred cubic centimeters. To prevent "osteoporosis from disuse" in the treatment of Colles' fracture, give 1 cc. of solution of parathyroid subcutaneously every third day for from three to five doses, in addition to the calcium gluconate powder by mouth.

In all fractures of large bones, all carpal and tarsal fractures and all fracture cases complicated with osteoporosis, give calcium gluconate powder as already stated. Also give a 10 cc. ampule of 10 per cent calcium gluconate daily intravenously for ten days, then every third day until the blood chemistry determinations indicate a serum calcium of from 11 to 12 mg. per hundred cubic centimeters. Increase the calcium level to 12 mg. per hundred cubic centimeters in cases of senile osteoporosis or in acromegalic types of bones. Give 1 cc. of solution of parathyroid subcutaneously every three days until the serum calcium has reached the desired level, which usually requires from five to seven doses. Then give 1 cc. every six to seven days until the bone



Fig. 4.—Section through a femur of a rat (81 days old) fed a diet deficient in both calcium and phosphorus but with fairly normal ratio. The zone of calcification is fairly normal in appearance but there is a delay in ossification.

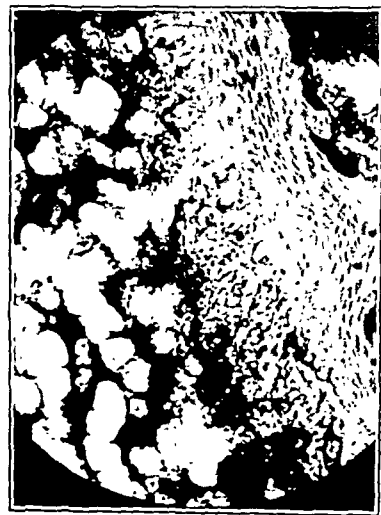


Fig. 5.—Section through a femur of a rat (81 days old) fed a diet low in calcium with the addition of vitamin D. Note the short bone trabeculae and the dissemination of fat cells throughout the bone marrow. This is very significant. It demonstrates the destructive effect of vitamin D in cases of low calcium diet.





calcium concentration. This increase in phosphorus concentration may decrease the ionized calcium to the degree of producing tetany. Parathyroid medication increases the excretion of phosphorus largely through diuresis beginning in one or two hours, resulting in an early increase in calcium ions even before the increase in serum calcium concentration takes place (from eight to twelve hours). Any diuretic such as hydrochloric acid, ammonium chloride or sodium chloride assists in the excretion of phosphorus.

It has been found that one large dose (1,000 units) of solution of parathyroid given to a rat would cause many of the bone cells of the femur to change into fibroblasts in the course of twenty-four hours and to change back into bone cells again within ninety-six hours.

We have observed in dogs that a short period of demineralization resulting from deficiency diets, prior to or at the time of fracture, followed by generous feeding, produces rapid healing. Deficiency diets continued for from six to seven weeks after fracture resulted in nonunion.

In man, a 1 cc. dose of solution of parathyroid given by hypodermic injection mobilizes calcium from the trabeculae for a few hours after admin-

istration. This is followed by rapid osteoblastic activity if sufficient serum calcium and serum phosphorus are available. We recommend the administration of 1 cc. of solution of parathyroid every third day for from three to five doses, then every seven days for five or more doses, according to the type of bone under management, as advised in the paragraph on medication for low calcium levels.

Our observations of the effect of therapeutic doses of solution of parathyroid in the treatment of more than a thousand fractures and several thousand medical cases in which hypocalcemia was a factor, as well as its gross and microscopic effects on bones of experimental animals, have resulted in certain definite conclusions. Solution of parathyroid given by hypodermic injection (1) increases the excretion of phosphorus in the urine,

(2) assists in the proper utilization of diffusible calcium, (3) probably makes some of the nondiffusible calcium available (more calcium ions) and (4) stimulates osteoclastic, followed by osteoblastic, activity in bone.

In cases of low serum calcium concentration there is no practical routine method of determining whether it is due to a dysfunction of the parathyroids or to an insufficient intake and absorption of calcium. We believe that in many cases all three factors are concerned. This is borne out clinically.

#### VITAMIN D

For centuries vitamin D in the form of cod liver oil has been used in the treatment of rickets, which is always due to a deficiency in serum phosphorus (fig. 2). Serum calcium levels may be normal, low or high. If there is a deficiency in both calcium and phosphorus, fewer pathologic changes of the bone result than in cases of phosphorus deficiency alone, as is demonstrated in figure 4.

Vitamin D increases the serum phosphorus concentration much more rapidly than the serum calcium, resulting in a short time in a low serum calcium-phosphorus concentration ratio. This may produce nonunion. The promiscuous use of vitamin D, especially viosterol, may be dangerous.

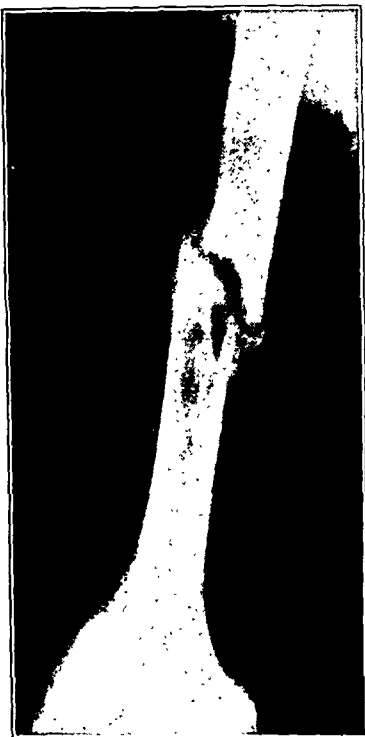


Fig. 9.—Mr. A. sustained a fracture of the middle third of the humerus in an automobile accident eleven months before coming to our clinic. The history and roentgen examination showed no improvement for five or six months. The Wassermann reaction was negative. Serum calcium was 8.8 mg. per hundred cubic centimeters and serum phosphorus 3.9 mg. at the time of the first examination. He was placed on a high calcium-low phosphorus diet, 1 drachm (4 Gm.) of calcium gluconate powder by mouth one-half hour before two meals each day, a 10 cc. ampule (10 per cent) of calcium levulinate intravenously daily for ten days, then every second day for ten doses. He was given 1 cc. of solution of parathyroid subcutaneously every third day for five doses, then once each week for five doses. After five weeks' medication, serum calcium was 11.4 mg. and serum phosphorus 3.8 mg. per hundred cubic centimeters. The urine was kept acid. The arm was not immobilized.

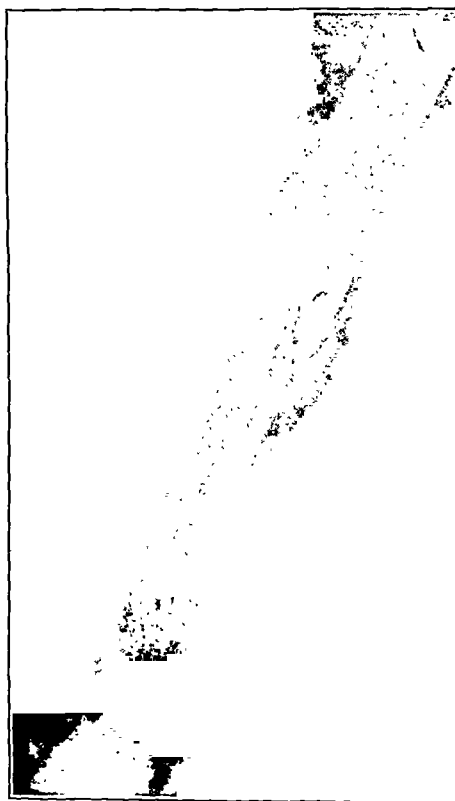


Fig. 10.—Union of the fracture sustained by Mr. A., complete eight weeks later. Patient was able to return to work.

We have shown that young rats on a calcium deficient diet with vitamin D (concentrated cod liver oil) develop marked osteoporosis. The bone is replaced by fat (fig. 5). Compere<sup>2</sup> has reported that vitamin D, even with extra calcium, delays union of fractures in some rats.

2. Compere, E. L.; Hamilton, B. and Dewar, M.: Influence of Vitamin D on Bone Repair: Healing of Fractures of Rachitic Bones, Surg., Gynec. & Obst. 68: 878-891 (May) 1939.

Extra vitamin D above a sustaining dose of from 400 to 500 units daily should be used only in cases of low serum phosphorus concentration, which constitute not more than 25 per cent of fracture cases. Moreover, vitamin D is not effective without a sufficient intake of phosphorus-containing foods. This fact has been almost completely overlooked in the treatment of rickets

and is responsible for failures even when large doses of vitamin D have been administered.

In the treatment of fractures in cases of low serum calcium alone one need not consider vitamin D medication. Most of these fractures will heal quickly enough so that vitamin D deficiency will not become a problem.

In cases of low phosphorus we have found that the administration of from 2,500 to 3,000 units of vitamin D daily is sufficient. This dose is continued until subsequent serum phosphorus determinations indicate the desired level of from 3.5 to 4 mg. per hundred cubic centimeters has been reached. We recommend the use of cod liver oil or halibut liver oil concentrate. The dose is easier to control with these preparations. In using more potent preparations of vitamin D there is more danger of over-medication, and some preparations are found to be toxic. The feeding of high phosphorus-containing foods is most important.

#### PH LEVELS

Minerals, especially calcium, phosphorus and iron, are absorbed mostly in the small intestine. Unless there is a sufficient amount of free hydrochloric acid in the stomach to neutralize partially the alkaline duodenum, minerals become insoluble

and pass through the intestinal tract unabsorbed. Calcium may combine with fats and form an insoluble calcium soap, and it may combine with the phosphates or oxalates and pass through the intestinal tract in these forms. Alkaline tissue suppresses calcium ionization.

In the management of fractures it is not practical to make a gastric analysis for free hydrochloric acid as a routine procedure. Unless the patient's history, such as one of ulcers or of burning, indicates hyperacidity, give from 15 to 20 drops of diluted hydrochloric acid in one-half glass of water during each meal. If the use of diluted hydrochloric acid for a few days causes definite gastric discomfort, it would indicate that the patient probably has a normal production of hydrochloric acid, and acid medication should be discontinued.

In order to minimize the danger of the precipitation of calcium in the urinary tract it is necessary to keep the urine definitely acid to litmus. Teach each patient the use of blue litmus paper.

Warn the patient against the use of too much citric acid fruit juices, bicarbonates, citrocarbonates and other alkaline powders.

To keep the urine acid it may be necessary to give ammonium chloride, which is best given in the form of  $7\frac{1}{2}$  grain (0.5 Gm.) enteric coated tablets. Give 1 or 2 tablets two or three times a day as necessary.

Unless there is already urinary stagnation with infection, the danger of the precipitation of calcium in the urinary tract is not a problem if the urine is kept acid.

#### THYROID

For many years the orthopedic surgeons have observed the beneficial effect of administration of thyroid in the treatment of some cases of delayed union. This is due to the establishment of normal oxidation of all tissues and not a direct effect on bone.

If one is treating a patient with definite evidence of osteoporosis or an acromegalic type of bone a basal metabolism test should be made, and if it is found to be below -10, the proper dosage of thyroid indicated in the case under management should be given.

Almost all hyperthyroid patients have hypocalcemia. Hyperthyroidism increases the excretion of calcium in the urine. It tends to produce hypocalcemia and osteoporosis. If the patient under management has definite signs of hyperthyroidism, give 10 drops of compound solution of iodine in a little milk with each meal, or from 3 to 6 tablets of diiodotyrosine daily for thirty days.

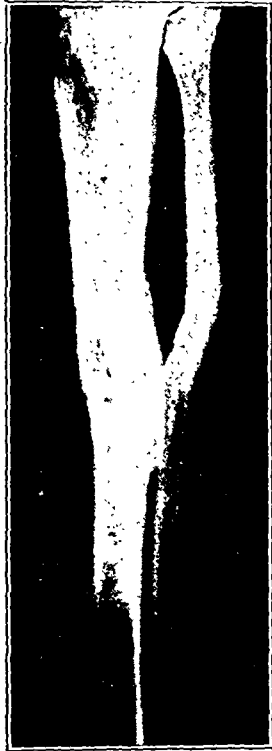


Fig. 11 (Mr. S., a miner aged 60).—The patient had sustained a fracture of both bones of a leg twenty-two months previous to coming to the clinic. There had been no improvement for many months. Note the fracture line through the osteoid tissue and demineralization of the entire bone. He was told ten years previous to fracture that he had gout and had been on a low protein (low phosphorus) diet for ten years. His serum calcium was 11.0 mg. and phosphorus 3.0 mg. per hundred cubic centimeters at time of first examination and the basal metabolic rate was -25. He was placed on a high phosphorus diet and 2,700 units of vitamin D daily, 3 grains (0.2 Gm.) of thyroid daily and given diluted hydrochloric acid by mouth.



Fig. 12 (Mr. S.).—Note the increased density of the entire bone in fourteen weeks. The patient returned to work at this time.

#### SUMMARY

Blood chemistry determinations should be made early in all fracture cases so that accurate medical management can be instituted immediately.

The object of this management is to establish a serum calcium concentration of from 10.5 to 12 mg. per hundred cubic centimeters and a serum phosphorus

concentration of from 3.5 to 4 mg. per hundred cubic centimeters with a ratio of 3 calcium to 1 phosphorus.

In addition to milk and calcium medication, the use of solution of parathyroid is suggested to assist in calcium metabolism, and in addition to a diet high in phosphorus the use of vitamin D is suggested to assist in phosphorus metabolism.

A normal amount of free hydrochloric acid in the stomach is necessary to assure the absorption of calcium and phosphorus, which takes place in the small intestine.

The precipitation of calcium in the urinary tract will not be a problem if the urine is kept acid.

It is understood that rapid union means early regeneration of bone—"healing by first intention"—without an excess of callus. Frequently roentgenologists will fail to report healing because of the small amount of callus apparent.

If accurate laboratory facilities are not available it is justifiable in all cases of fracture to institute the medical management recommended in cases of low serum calcium, as at least 85 per cent of all cases of fracture present a low serum calcium.

Since accurate medical management in all cases of fracture has been instituted we have not had a failure in union of fresh fractures, have been able in many cases referred to the clinic to regenerate delayed union, have obtained earlier results and have had fewer cases of permanent disability.

9615 Brighton Way.

## PELVIC SYMPTOMS OF URINARY TRACT ORIGIN

PRESTON T. BROWN, M.D.

AND

JOHN W. PENNINGTON, M.D.

PHOENIX, ARIZ.

The most common presenting symptoms of gynecologic patients are chronic lower abdominal pain and backache. These are usually, but often erroneously, interpreted by the patient as being due to abnormalities of the genital tract. This self-made diagnosis of ovarian or uterine disease too often finds concurrence in the opinion of the surgeon and repeatedly leads to unnecessary and harmful operations. Many, if not a majority, of the pains referred to the lower part of the abdomen and back are not due to genital disorders but are the results of orthopedic defects, gastrointestinal disturbances, or abnormalities of the urinary tract. For many years Hunner has been emphasizing the important relationship between urinary tract conditions and obscure pelvic symptoms. He has stressed the symptom complex of the stricture of the ureter and has repeatedly demonstrated the relief of those symptoms by appropriate treatment.

Genital disease may be simulated by ureteral stricture, stricture of the urethra or contracture of the vesical orifice, chronic urethritis and trigonitis, and rarely by ptosis of the kidney. Although Hunner has been teaching and demonstrating these facts for many years, there are still many of his colleagues who have not as yet accepted his work, including outstanding teachers of gynecology and urology who do not believe that

ureteral stricture produces pelvic symptoms. As a result of this skepticism a large number of medical students pass into practice each year without knowledge concerning this important subject. This discussion is therefore presented, not as original work, but in support of the observations of Hunner, David M. Davis and others as to the importance of mild and obscure forms of urinary obstruction and as a reminder, to the surgeon and gynecologist, of the fact that a woman has a urinary tract.

Correct diagnosis of obscure pelvic symptoms requires the correlation of a painstaking history with careful gynecologic and urologic examinations, including exploration of the urinary tract by means of x-rays and cystoscopy.

### SYMPTOMATOLOGY

Many women in whom urinary tract pathologic conditions are later shown to exist complain only of symp-



Fig. 1 (case 3).—Retrograde pyelogram showing stricture of both ureters.

toms which are described as neurotic: particularly constant nervous tension, attacks of hysteria, paranoid feelings and depression. Frequently these are the only complaints, and a careful history is required to bring out symptoms suggesting an origin in the pelvis or urinary tract. We are convinced that a diagnosis of neurasthenia is untenable until urologic examination has ruled out stricture of the ureter.

Dysmenorrhea, while not frequently a result of urinary tract disease, may be caused by ureteral stricture. In such cases the cramps are often of an acquired type, especially in a dysmenorrhea developing for the first time after parturition. The pain may be unilateral and it is usually described as deep in the pelvis, frequently accompanied by sacral or lumbar backache.

Unilateral and bilateral lumbar and sacral backache is in many cases the result of stricture of the ureter, ptosis of the kidneys or any of the several urethral and bladder conditions mentioned.

Gastrointestinal symptoms, such as indigestion, chronic constipation and flatulence, have been found by Hunner and others to result from ureteral strictures. A sensation of prolapse and pressure in the pelvis, without actual descensus, is strongly suggestive of some bladder or ureteral disorder. When one considers the



Fig. 2 (case 4).—Intravenous urogram showing stasis and dilatation of both ureters due to stricture.

numerous patients with actual prolapse of the uterus who do not experience this symptom, the deduction is inescapable that something more than mere displacement must exist as the cause. It is necessary in all history taking to cross examine for any slight frequency, nocturia or painful urination, since these are accepted by most women as part of life's normal burdens and are not voluntarily mentioned. Of great significance is the patient's report of previous long continued unsuccessful gynecologic therapy. A woman whose uterus has been suspended, ovaries removed or resected, or on whom an appendectomy has been performed in order to relieve pain which still persists after the operation is almost certain to have some urinary tract difficulty. These symptoms will be illustrated in the case reports to follow.

#### PHYSICAL EXAMINATION

Abdominal examination in cases of ureteral stricture usually reveals tenderness in the region where the ureter crosses the brim of the pelvis. One or both kidneys may be palpable and are often tender. Examination of the patient in the upright position should not be omitted. The pelvic examination is striking because of the absence of gross pathologic change. Too frequently retroversion and cystic ovaries are assumed to be the cause of lower abdominal and back pains, of which they may be entirely innocent. Tenderness of the ureter as it passes through the pelvis is readily confused with adnexal tenderness and usually may be differentiated by Hunner's technic of palpating the ureter lateral to the cervix.

#### LABORATORY EXAMINATION

Urinalysis in patients of the type described is of surprisingly little assistance, since frequently pus and bacteria are absent in the stained sediment. It should be recognized that serious disease of the urinary tract may exist without evidences of the trouble in the urinalysis. In the presence of a urethritis or trigonitis numerous epithelial cells may be present, and in about half of these micro-organisms are found.

Urography, on the other hand, is of vital importance in establishing the diagnosis. We have used the intravenous method most commonly and have found it usually satisfactory when the bowels have been emptied by the preliminary use of castor oil. Exposure in the vertical, as well as the horizontal, position is essential. We have often been in disagreement with the roentgenologists and clinicians in interpretation of the films. Gross hydronephrosis, ureterectasis, kinks and strictures of the ureter are readily acknowledged, but minor degrees of these conditions the roentgenologist is inclined to declare within normal limits, while we have proved them to be significant in the light of subsequent clinical observations and progress.

#### UROLOGIC EXAMINATION

When the passage of a 16 F. urethral catheter meets resistance or causes discomfort, one is justified in assuming the presence of narrowing or irritation. Determination of the bladder capacity should be part of the routine examination. Reduction of the capacity

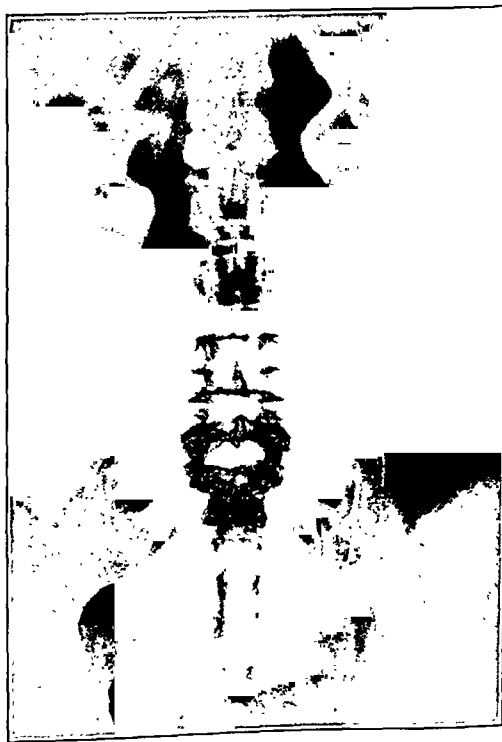


Fig. 3 (case 5).—Intravenous pyelogram showing the right kidney in normal position but the pelvis slightly dilated.

below 300 cc. is significant and should stimulate a diligent search for the cause. When the complaints of pressure and bearing down in the lower part of the abdomen are accompanied by discomfort on passage of a soft rubber catheter and by a decreased bladder capacity with sterile urine, a presumptive diagnosis of urethritis and trigonitis is made. Urethral stricture, chronic

trigonitis and urethritis are so commonly associated that often they cannot be separated into clinical entities. Endoscopic examination of the bladder may show no definite abnormalities, but prominence of the muscle bundles, even true trabeculation, is frequently presented and is significant of urethral obstruction. The trigon

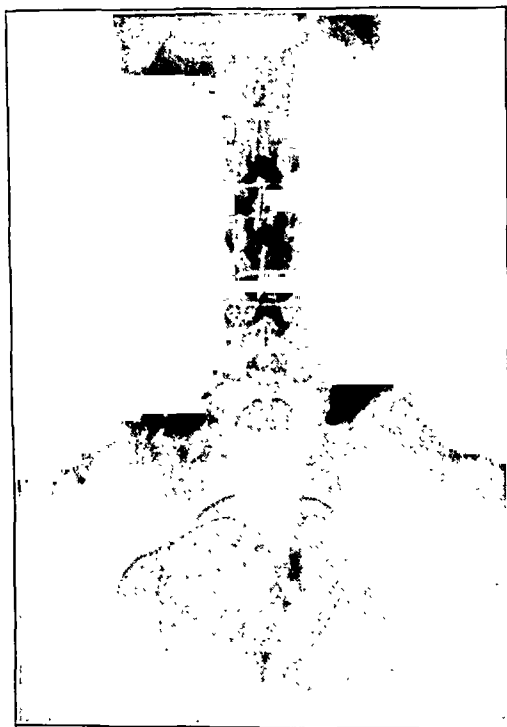


Fig. 4 (case 5).—In the upright position the right kidney is found much lower.

may show a simple congestion or fine granular or papillary excrescences. On withdrawing the endoscope through the bladder neck, one may easily see the constriction, and changes similar to those of the trigon may continue to the midportion of the urethra. The ureteral orifices may be smaller than normal and the surrounding membrane show slight congestion in the presence of stricture higher in the ureter. In a few instances minor degrees of ureterocele are found. The passage of bulbs up the ureters is resisted in one or more areas, and withdrawal is accompanied by a "hang" at these points. The reproduction of the particular type of pain of which the patient complains is frequently elicited when the stricture is stretched by the bulb. The well known appearances in hydronephrosis will not be overlooked by one who is on the alert for stricture of the ureter.

#### REPORT OF CASES

**CASE 1.—Urethral stricture and contracture of the bladder.** Mrs. C. L., aged 23, had been delivered by low forceps after a mild toxemia of pregnancy. Convalescence was uneventful, but on resumption of normal activity a pronounced low backache developed. Questioning revealed nocturia (from three to four voidings) with daytime frequency at forty-five minute intervals. Pelvic examination revealed no abnormalities of the genitals. The catheterized specimen of urine showed no red blood cells or infection; the bladder capacity was 375 cc. Three treatments, consisting of bladder distentions and irrigations, dilation of the urethra and instillation of 0.25 per cent silver nitrate, entirely relieved the patient of both backache and frequency.

**CASE 2.—Urethral stricture and contracture of the bladder.** Mrs. O. L., aged 34, complained of vaginal irritation with discomfort in the lower part of the abdomen and nocturia (from one to two voidings). The appendix and the left ovary had been removed six months before, and later the cervix had been cauterized but no relief was obtained. Examination revealed no evidence of pelvic abnormality. The urethra was found to be small and irritable; the bladder capacity was 300 cc. The urine was normal. The urethra required dilation before endoscopic examination. The bladder showed definite trabeculation, and the vesical orifice was small and contracted. Fine granular changes appeared over the trigon and inner urethra, accompanied by congestion. Hydraulic distentions and dilation of the urethra, at weekly intervals, effected a cure in six weeks' time. The bladder capacity was increased to 500 cc., and the urethra could be easily dilated to 33. In addition to the relief from physical discomfort, including nocturia, the patient noted also the release from nervous tension. Yearly treatments have maintained her normal health.

**CASE 3.—Ureteral stricture.** Mrs. A. P., aged 25, complained chiefly of constant pain in the left side of the abdomen, with exacerbation during the menses. She had had three full term pregnancies, twenty-two months having elapsed since the third one. One year before, although pyelograms made (fig. 1) had shown abnormalities, the appendix had been removed, but the pain on the left side remained unaffected. Some urinary frequency was present and some tenderness in the left lower quadrant, which seemed to be at the point where the left ureter crossed the brim of the pelvis. Pelvic examination showed no evidence of genital disease. There was very marked tenderness lateral to the uterus, pain being elicited by pressure on the lateral wall of the pelvis. A catheterized specimen of

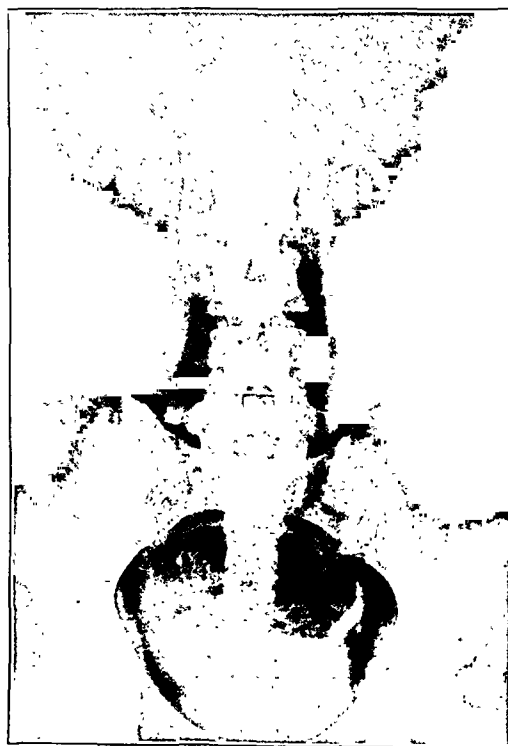


Fig. 5 (case 6).—Urogram shows the stasis and dilatation which had not been suspected before the picture was taken.

urine was negative. After three cystoscopic examinations, with dilation of the left ureter to a 10 F. bulb (no larger bulb could be passed), the patient was free from pain. She could dance, which was something she had been unable to do for the past year, and she has felt so well that she has not yet returned for dilation of strictures in the right ureter revealed by x-ray examination.

CASE 4.—*Ureteral stricture.* Mrs. R. E., aged 19, complained chiefly of severe cramplike pains in the right side accompanying menstrual periods, present since the onset of menses and especially severe during her high school years. Additional symptoms were low backache, pain in the right lumbar region and intermenstrual cramplike pain in the pelvis. There were no

CASE 6.—*Ureteral stricture.* Miss A. G., aged 44, complained of weakness, fatigue, pressure in the perineum and pronounced cramps during menstruation. For two months preceding her first visit pelvic pain had also been present during the intermenstrual periods. Pelvic examination was done under general anesthesia because of an intact hymen and showed perfectly normal pelvic organs. Because the description of the patient's cramps seemed to direct attention only to the uterus, endocrine therapy was tried, but without success. Urologic examination was then carried out, in spite of negative results in the catheterized urine. The urethra was tender to catheterization; the bladder capacity was 150 cc. Dilatation of the urethra was necessary before the endoscopic examination could be done. This disclosed slight congestion of the bladder and granular excrescences in the urethra. Hydraulic distentions of the bladder, dilation of the urethra and application of silver nitrate effected only partial relief of symptoms. An intravenous pyelogram was therefore made, with results as shown in figure 5. After dilation of the ureters the patient's cure was complete.

CASE 7.—*Ureteral stricture.* Mrs. G. D., aged 35, divorced, complained of aching of several years' duration in the right lower quadrant of the abdomen, which had led the patient to submit to removal of the appendix, suspension of the uterus and a subsequent pelvic exploration. She stated that her discomfort was relieved by voiding. There was no nocturia but some frequency during the day. Many attempts at medicinal treatment, including endocrine therapy, had proved futile. A catheterized specimen of urine was negative; the bladder capacity was 390 cc. The appearance of an intravenous urogram is shown in figure 6. After dilation of the right ureter to a No. 12 F. bulb, the patient regained normal health.

CASE 8.—*Ureteral stricture.* Mrs. O. B., aged 41, complained of a bearing down pain with occasional colic in the suprapubic



Fig. 6 (case 7).—This hydronephrosis is due to stricture of the ureter, which had been present for years.

gastrointestinal disorders and no dysuria. Tenderness was found in the right lower quadrant, median to McBurney's point and too high for the tubo-ovarian region. A catheterized specimen of urine showed an occasional gram-negative bacillus and gram-positive coccus. The appearance of an intravenous pyelogram is shown in figure 2. At cystoscopy the bladder was normal; the right ureteral orifice was slightly congested. This ureter could not be dilated above a No. 8 F. bulb at the initial treatment, which was followed by the first painless menstrual period the patient had ever experienced. The ureter was subsequently dilated to a No. 12 F. bulb. One year later the patient returned with slight recurrence of menstrual cramps. These were relieved by a single treatment and for the past year and a half the patient has been free from pain.

CASE 5.—*Ureteral stricture.* Mrs. A. M., aged 39, had been under observation for several years, during which time multiple myomas of the uterus had developed, concurrent with severe lower backache. Because the tumors were impacted deep in the cul-de-sac, it was believed that a hysterectomy would relieve the backache and this operation was accordingly performed. After an uneventful convalescence not only was the sacral backache still present but this affected area had spread to include the right lumbar region. A catheterized specimen of urine showed no bacteria, pus or red blood cells. Intravenous pyelograms (figs. 3 and 4) revealed ptosis of the right kidney with slight dilatation of the ureters and some filling defects. Cystoscopic examination showed the ureteral orifices slightly congested but normal in size. Resistance was encountered in each ureter to a No. 8 F. bulb in the intramural portion and 5 cm. higher. After the ureters had been dilated to a No. 12 F. bulb all pain disappeared and the patient's general health showed marked improvement.



Fig. 7 (case 8).—Double ureter on the left, ureterectasis and ureterocoele on the right.

region over a period of ten years. There were some frequency of urination and radiation of pain into the left lumbar region. In spite of symptoms pointing to the urinary tract, the patient had been subjected to removal of the appendix and suspension of the uterus, without relief. Pelvic examination showed no evidence of abnormality. The urethra was contracted; the bladder capacity was 325 cc. The results of an intravenous



pyelogram are shown in figure 7. The details are not as clear as we would wish, but on the left side two kidney pelves can be seen and two ureters merging into one close to the bladder wall. Marked dilatation of the lower right ureter is apparent, a large ureterocele, which is clearly identified as a negative shadow on the more dense bladder shadow. Cystoscopic examination showed but one ureteral orifice, on the left side, while the right side presented a large cystic mass approximately 15 mm. in diameter. This increased and decreased in size with each efflux of urine. Treatment in this case consisted of incising the ureterocele and dilating the left ureter to a No. 12 F. bulb. The patient was entirely relieved of symptoms and has continued in good health. The last examination revealed no vestige of the ureterocele, and there was no resistance to bulbs on that side.

#### CONCLUSIONS

Obscure abdominal pain is frequently produced by disease of the urinary tract, in many instances accompanied by few or by no manifestations pointing to its true origin. Diseases of the urethra and bladder, and especially stricture of the ureter, produce many varied symptoms. The responsibility for correct diagnosis rests on the surgeon and gynecologist whom such patients usually consult. The dismal failure of pelvic surgery in these cases reflects unfavorably on the whole field of operative gynecology. Unfortunately the operating surgeon rarely sees the end results of his failures, as the patients seek help elsewhere. It is therefore incumbent on the surgeon to make a careful study of the urinary tract before ascribing obscure pelvic symptoms to uncomplicated retroversion, cystic ovaries, chronic cervicitis or even more clearcut forms of pelvic disease.

#### ABSTRACT OF DISCUSSION

DR. GUY L. HUNNER, Baltimore: The authors render a real service by emphasizing the fact that now, after twenty-five years of many reports similar to theirs, coming from hospitals in all parts of the world, "many of our medical students pass into practice each year without knowledge concerning this important subject." If one turns to one of the best and most recent textbooks on gynecology, produced in 1938 by Arthur Curtis, one will find excellent chapters on backache, dysmenorrhea and dyspareunia, in none of which is mentioned ureteral stricture, the primary cause of the symptoms in many of these unhappy and troublesome cases. The gynecologist who leaves out of account this important lesion is rendering false diagnoses and fruitless treatment in at least 50 per cent of his cases in which backache is complained of. I think a conservative estimate on his cases of dysmenorrhea would almost reach this same figure. In his cases of dyspareunia, if those apparently due to some psychic repulsion and those manifestly due to some lesion about the external genitalia, the vagina, the cervix and the uterine ligaments are excluded and only those cases which in the past have given so much trouble in diagnosis are included, it would be found that most of them are of urologic rather than gynecologic origin. As the authors have said, the surgeon and gynecologist must bear in mind that the woman complaining of a symptom the cause of which is not at once manifest has a urinary as well as a genital tract. The failure to make a correct diagnosis in this large group of patients is the more inexcusable because of the ease with which one can decide whether the urinary tract is at fault. When it becomes established practice in gynecology to palpate carefully along the entire urinary tract, particularly over the juxtavesical portion of the ureter, and in doubtful cases to use a bulb on the diagnostic catheter and the Kelly differential test for pain by slightly distending the kidney pelvis, many problems in diagnosis which have seemed baffling will become simple. Many of the newer operations, such as sympathectomy, presacral neurectomy and the more recent alcohol injection of Frankenhäuser's plexus for the "broad ligament neuritis" of James Young and his followers in Britain, all

designed to further the well-being of the patient, will lose much of their popularity because of the more logical, simple and effectual methods of treatment when a correct diagnosis is established.

DR. I. W. KAHN, New York: About ten years ago I published a paper in the *American Journal of Obstetrics and Gynecology* stressing the importance of a urologic examination of every gynecologic patient. At present, in my department, the Female Cystoscopic Department of the New York Post-Graduate Hospital, every patient who is admitted for a gynecologic checkup is automatically sent to the Female Cystoscopic Department for a urologic investigation. At another organization I presented about sixty slides of urologic pathologic conditions that we found in patients who had practically no urologic symptoms. From this presentation one of the doctors present thought I was a practicing urologist instead of a gynecologist. I told him that every one of those conditions—stones, stricture, hydro-nephrosis, tumors, tuberculosis, and so on—were all found in patients who went through a routine urologic checkup. It is simple to give a patient such a checkup. The examining cystoscope today is no more to us than a thermometer and the stethoscope. The bladder of every patient who comes into the gynecologic clinic is looked at and if necessary we do an intravenous and retrograde pyelogram as well as catheterization of both ureters. Another interesting thing that we do in obstetrics is to inject 20 cc. of diodrast intravenously, and it is remarkable how quickly one can get knowledge about the ureters and kidneys of patients whose urologic system is not acting according to normal. I suggest that the diodrast investigation be considered for obstetric patients. It is a simple procedure.

DR. PRESTON T. BROWN, Phoenix, Ariz.: The title of this paper is somewhat misleading in that the symptoms enumerated are not truly pelvic symptoms at all; they are urinary tract symptoms. They are so closely related and so closely simulate genital symptoms that they are repeatedly mistaken for gynecologic conditions by the patient, and they are also mistaken by the gynecologist as well as the surgeon. It is especially true that the surgeon mistakes these for pelvic conditions when he finds these slight anatomic and mechanical variations from the usual pelvic anatomy, such as movable retroversions, cystic ovaries and the uterus placed lower or farther back in the pelvis than normal. The complete gynecologist must survey many specialties from psychiatry to proctology, but if he is to afford women the most effective service he must combine with his gynecology, above all else, urology. All practitioners command the information obtained from the catheterized urine specimen, calibration of the urethra and determination of the capacity of the bladder. Dr. Hunner mentions that the intravenous pyelogram is in most cases satisfactory for the diagnosis of mild and obscure forms of ureteral obstruction. It does, however, require a carefully made picture and an interpretation that is different from that of the usual roentgenologist. Many of the x-ray men look at our pictures and say they show normal urinary tracts, and indeed one can obtain better pictures by the retrograde procedure. However, for the noncystoscopic gynecologist the availability of the intravenous method is very tempting. The patients who have been described in the paper are selected from a large group of other similar patients found in a small town gynecologic practice, and if one hunts for them one will find them everywhere.

**Individual Differences.**—Because of the unique combination of ancestral traits that appears in each individual, there are differences between children in the same families. In no one person do we see realized all the potentialities with which he was endowed at birth. There are present in each individual many possibilities that will never be utilized by the forces surrounding that person. The effect of environment is to weed out some traits and to emphasize others. Difficulties or lacks are often exaggerated by the circumstances of the individual's life. Recognition of the individual differences to be found in each family of children may lead to planning an environment which stimulates to a greater extent the individual characteristics and potentialities of each child.—Faegre, Marion L., and Anderson, John E.: Child Care and Training, Minneapolis, The University of Minnesota Press, 1940.

HYPERTENSION ASSOCIATED WITH  
UNILATERAL RENAL DISEASE

REED M. NESBIT, M.D.

AND

RIGDON K. RATLIFF, M.D.

ANN ARBOR, MICH.

Recent advances in our knowledge of the underlying causes of hypertension are increasing the interest of the entire medical profession in that often fatal disease.

Evidence is accumulating which suggests that many patients with essential hypertension may be improved or perhaps cured by neurosurgical operations. In this group of patients the neurophysiologic background of the disease is little understood, and certainly the manner in which improvement or cure is effected after operation has not been elucidated. Certain failures after these operations may occasionally be traced to errors in diagnosis in that the hypertension is not of the

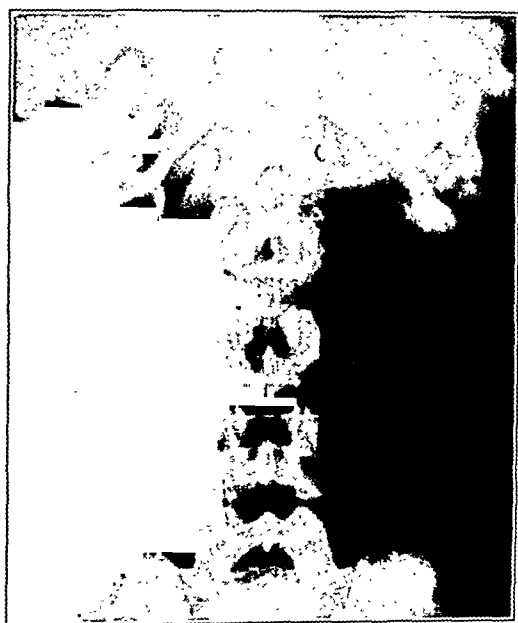


Fig. 1 (case 1).—Intravenous pyelogram showing marked hydronephrotic changes of the left kidney. Normal right kidney.

so-called essential type but is found to result from a definite organic lesion.

Since Goldblatt's demonstration of a renal origin for hypertension clinicians have sought to demonstrate a causal relationship between various organic lesions of the kidney and abnormal elevations of the blood pressure. The clinical demonstration that such causal relationships do exist has opened up a new field of investigation and has shown the necessity of including a complete urologic study in the investigation of any hypertensive patient. We now know that many patients formerly described as having essential hypertension show gross lesions of one or both kidneys, which in many instances can be demonstrated to be the cause for the hypertension. An enumeration of all of the gross renal lesions responsible for hypertension cannot be made at this time and must await further clinical

investigations, but certain phases of the problem which appear to warrant positive conclusions may be profitably discussed.

## EXPERIMENTAL EVIDENCE

Goldblatt<sup>1</sup> has demonstrated that ischemia of the kidney produced by partial occlusion of the renal arteries results in an elevation of the blood pressure in laboratory animals. In the dog, unilateral renal ischemia with the opposite kidney intact and normal produces an elevation of blood pressure which is always transient and which never goes into the malignant form. Return of the blood pressure to normal is thought to be the result of the development of collateral circulation in the ischemic kidney. This view is supported by the fact that unilaterally ischemic kidneys which are wrapped in a cellophane membrane at the time the vessels are clamped always produce a permanent hypertension. Removal of the unilaterally ischemic kidney or the constricting arterial clamp is always followed by a return of the blood pressure to the normal level. Removal of the normal kidney with the opposite kidney ischemic results in permanent hypertension.

Bilateral renal ischemia in the dog produces permanent hypertension. Goldblatt reported that moderate bilateral arterial constriction produces a permanent benign hypertension. Removal of the arterial constriction in the group of animals with this condition results in a lowering of the blood pressure to normal, gradual after removal of constriction from one kidney and abrupt after simultaneous removal from the two kidneys. Excessive bilateral arterial constriction results in malignant hypertension, which invariably terminates fatally with the animals dying of renal insufficiency. In these animals the malignant phase of hypertension is heralded clinically by impairment of renal function as demonstrated by the urea clearance test and is demonstrated pathologically by parenchymatous changes of cellular necrosis in the kidneys with or without hemorrhage, while other organs of the body show widespread arteriolar necrosis and necrotizing arteriolitis. Dogs with benign hypertension have not shown any of these pathologic changes. In the animals showing clinical signs of malignant hypertension, i. e. having impairment of renal function, removal of arterial constriction from one or both kidneys has failed to relieve the hypertension and has not altered the fatal course of events, demonstrating that the pathologic changes of malignant hypertension observed in these experiments are irreversible.

Wilson and Byrom<sup>2</sup> have recently shed further light on this subject. Working with rats, they found that unilateral renal ischemia frequently produced permanent hypertension. In animals with this condition they recognized two main types of change clinically and pathologically.

The first type comprised those in which the blood pressure rose gradually over a period of several weeks to reach a steady high level which, in animals still under observation, had been maintained for nine months. These animals appeared clinically to be in normal health.

The second type comprised those in which the hypertension ran a more irregular course and often led to a state of great weakness, wasting, coma and occasionally convulsions and terminated in death. These symptoms were not considered due to renal insufficiency, for the blood urea was within normal limits, and removal

1. Goldblatt, Harry: Studies on Experimental Hypertension: XII. The Experimental Production and Pathogenesis of Hypertension Due to Renal Ischemia. *Am. J. Clin. Path.* 10: 40-72 (Jan.) 1940. (This article gives a complete Goldblatt bibliography.)  
2. Wilson, Clifford, and Byrom, F. B.: Renal Changes in Malignant Hypertension. *Lancet* 1: 136 (Jan. 21) 1939.

From the Department of Surgery, University of Michigan Medical School.

Read before the Section on Surgery, General and Abdominal, at the Ninety-First Annual Session of the American Medical Association, New York, June 13, 1940.

of the ischemic kidney was sometimes followed by rapid clinical improvement with return of the blood pressure to normal.

The pathologic changes noted in this second group of animals are of interest.

The ischemic kidney often presented no macroscopic or histologic abnormality; more often diffuse tubular atrophy was evident, all degrees being observed from slight to severe. Partial infarction of the kidney was not uncommon. Acute glomerular and arterial lesions such as occur in the opposite kidney were not observed.

In the opposite kidney microscopic changes were present which closely resembled those of malignant hypertension in man. The lesions were focal in distribution, glomeruli, tubules and interstitial tissue showing changes closely associated with acute arterial and arteriolar necrosis. Acute arterial lesions similar to those observed in the unclamped kidney were observed in the pancreas, intestine, stomach and heart and more rarely in the adrenal glands, liver and testes. Wilson and Byrom expressed the belief that, since only one kidney is operated on, renal insufficiency is an unlikely factor in the etiology of the vascular lesions observed. This conclusion appears to be supported by the absence of nitrogen retention in their animals. The fact that the lesions do not occur in the clamped kidney appears to indicate that they are not due to a circulating toxin or pressor substance and that they are not due to simple ischemia. Wilson and Byrom also expressed the belief that the production of the lesions is related in some way to the increased intra-arterial tension from which the ischemic kidney is protected by the clip on the renal artery. They suggested that the determining factor is probably a sudden strain imposed on the vessel wall by the combination of severe vasoconstriction and the resultant rapid rise in blood pressure. This could presumably produce a vascular necrosis which in the case of a gradually rising pressure might be prevented by the development of compensatory hypertrophy of the arterial wall.

It is of great interest that whereas Goldblatt's dogs, having what he termed malignant hypertension produced only by bilateral renal ischemia, showed no clinical improvement after removal of the arterial clamps, in Wilson and Byrom's experiments rats that showed clinical symptoms of weakness, wasting, coma and convulsions with hypertension after the production of unilateral renal ischemia have shown recovery from all symptoms and have regained normal blood pressures after removal of the clamped kidney.

These differences which have been observed between dogs and rats have not yet been explained. One wonders to what extent conditions in man might parallel the observed changes in either or both of these animals. An answer to this question would be of great clinical importance. Laboratory investigations with other animals should be made to elucidate many points of clinical importance.

#### CLINICAL EVIDENCE

Recent clinical investigations have suggested that many non-nephritic types of renal lesion may be associated with hypertension. The causal relationship in many instances is not clearly evident; however, there appear to be three definite types of kidney lesions in which the relationship to hypertension is evident:

1. Gross occlusion of one or more arteries leading to the kidney has been observed to produce clinical hypertension in man and in this instance has closely paralleled the experimental work of Goldblatt. Two

cases of this unilateral type have been reported in which removal of the diseased kidney resulted in cure of the hypertensive state. In Leadbetter and Burkland's<sup>3</sup> case renal ischemia resulted from partial occlusion of the renal artery by a plug of aberrant muscle, apparently congenital in origin. In the case reported by Boyd and Lewis<sup>4</sup> the ischemic kidney contained an infarct which involved about one third of the organ. The recently reported observations of Blackman<sup>5</sup> may be of far-reaching importance in our understanding of so-called essential hypertension. He studied autopsy material from 50 patients who died in Johns Hopkins Hospital with a diagnosis of essential hypertension. Arteriosclerotic changes producing partial occlusion of the main renal arteries were found in 86 per cent of these cases, while only 5 per cent of a control series who had no clinical hypertension showed these gross vascular changes.

We have, in a previous communication, pointed out the possibility of renal ischemia with hypertension resulting from trauma of the kidney, reporting a case

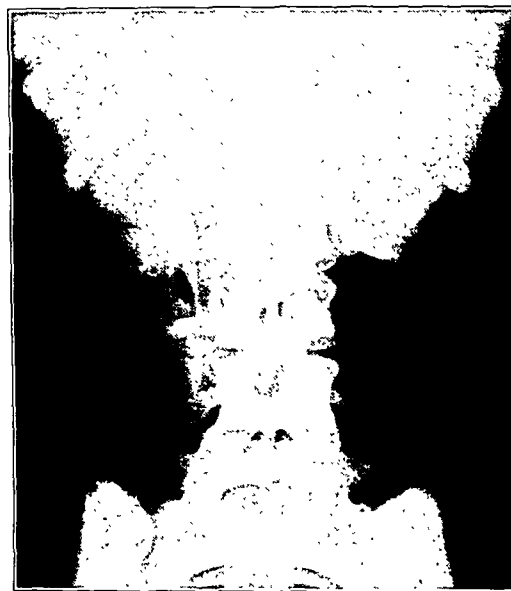


Fig. 2 (case 2).—Intravenous pyelogram showing nonvisualization of the left kidney; the right kidney is normal with hypertrophy.

in which malignant hypertension developed in a patient who had previously had a severe injury to one kidney resulting in an infarction of about one third of the organ. Sterling<sup>6</sup> has observed elevated blood pressure in experimental animals having gross traumatic renal lesions.

2. The association of hypertension with urinary obstructions has been long recognized clinically. Experimental evidence has supported this observation in that unilateral or bilateral ureteral ligation has resulted in the production of elevated blood pressures in laboratory animals.<sup>7</sup> A possible explanation for hypertension produced in this manner may well lie in the experimental

3. Leadbetter, W. F., and Burkland, C. E.: Hypertension in Unilateral Renal Disease, *J. Urol.* **39**: 611 (May) 1938.

4. Boyd, C. H., and Lewis, L. O.: Nephrectomy for Arterial Hypertension, *J. Urol.* **39**: 627 (May) 1938.

5. Blackman, S. S., Jr.: Arteriosclerosis and Partial Obstruction of Main Renal Arteries in Association with "Essential" Hypertension in Man, *Bull. Johns Hopkins Hosp.* **65**: 353-375 (Nov.) 1939.

6. Sterling, W. C.: Verbal communication to the authors.

7. Hartwich, Adolf: Der Blutdruck bei experimenteller Urämie und partieller Nierenausscheidung, *Ztschr. f. d. ges. exper. Med.* **60**: 462, 1930. Harrison, T. R.; Mason, M. F.; Resnik, H., and Ranney, J.: Changes in Blood Pressure in Relation to Experimental Renal Insufficiency, *Tr. A. Am. Physicians* **51**: 280, 1936. Bell, E. T., and Pedersen, A. A.: The Causes of Hypertension, *Ann. Int. Med.* **4**: 227 (Sept.) 1930.

studies of Hinman<sup>8</sup> on the pathogenesis of hydronephrosis. He demonstrated that hydronephrotic atrophy of the renal parenchyma results not primarily from increased intrapelvic pressure but from ischemia with a progressive obliteration of the intrarenal vascular supply. The relative infrequency with which hydronephrosis is associated with hypertension may be explained



Fig. 3 (case 2).—Section of right kidney showing normal anatomy with exception of postmortem changes.

by the development of collateral circulation in the kidney which has been demonstrated to occur in the presence of the obstructive uropathies.

We have observed three cases in which hydronephrosis was associated with hypertension and in which the blood pressure returned to normal after appropriate management of the obstructive lesion. Two of these cases have been previously reported<sup>9</sup> and the third is herewith presented:

CASE 1.—G. P., a man aged 20, a university student (fig. 1), complained of intermittent attacks of severe pain in the region of the left kidney for three years. Attacks occurred at frequent intervals and were of two to three days' duration. The patient was known to have had hypertension for three years. (Observations were made at the University Health Service.)

Examination revealed acute tenderness of the left costovertebral region with muscular spasm on admission. Physical examination otherwise was normal except for blood pressure, which was 180 systolic and 90 diastolic. The urine showed a few red cells but no other abnormality. The blood nonprotein nitrogen level was 27.8 mg. per hundred cubic centimeters. Excretory urograms showed a normal right kidney and 3 plus hydronephrosis of the left kidney.

Excision of the left kidney was performed Jan. 18, 1940. A large hydronephrotic sac was removed.

The pathologist's report revealed advanced hydronephrotic atrophy.

Postoperative convalescence was normal, the blood pressure attaining a normal level immediately after operation, where it has remained to date. The highest reading during the postoperative period thus far was 134 systolic and 79 diastolic.

3. The other condition which has been more frequently observed to be associated with hypertension is chronic pyelonephritis. Longcope<sup>10</sup> followed 22 cases of bilateral chronic pyelonephritis for a long period of

time. In 10 of 15 cases which he followed to advanced or terminal stages, clinical hypertension developed. The hypertensive patients which he observed all had demonstrable reduction of renal function, and he tended to associate the occurrence of renal insufficiency with that of hypertension. Pathologic examination of tissues after death in this series failed to disclose any important or constant vascular changes which Longcope could consider responsible for the clinical hypertension.

Butler<sup>11</sup> reported on observations carried out in a series of 15 children having chronic pyelonephritis with associated hypertension. In these cases impairment of renal function was not observed coincidentally with the onset of hypertension. Pathologic material from 3 of the patients disclosed marked arteriolar thickening within the diseased kidneys. In 2 of the cases reported by Butler there was hypertension associated with unilateral chronic pyelonephritis, and nephrectomy is reported to have cured both patients. Numerous cases have been reported in the recent literature<sup>12</sup> in which unilateral chronic pyelonephritis with associated hypertension has been submitted to nephrectomy. In most of the cases reported, an improvement or cure of the hypertension appears to have followed operation. Factors which may militate against a favorable outcome in such cases may be either the presence of an extrarenal cause for the hypertension or a vascular lesion of the surviving kidney which tends to perpetuate the hypertension.

Time and space do not permit a detailed account of the 12 patients we have observed having obvious unilateral chronic inflammatory lesions of the kidney associated with hypertension. Most of the cases have been previously reported. Ten patients have been operated on, while in 2 the diagnosis has been established by autopsy.

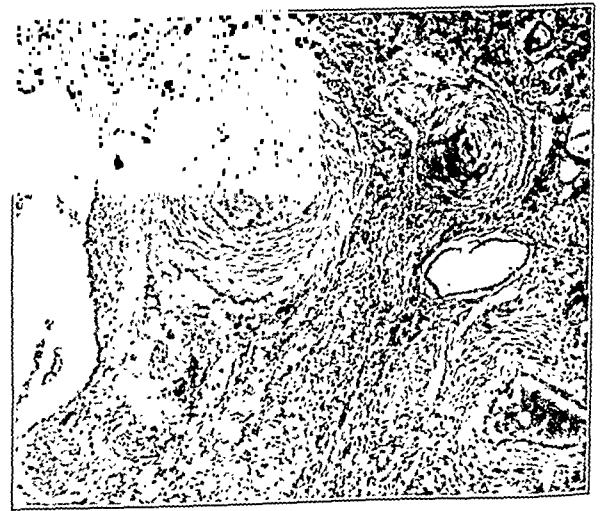


Fig. 4 (case 2).—Section of left kidney showing marked inflammatory changes and vascular sclerosis.

Three cases are herewith presented because they illustrate certain points of interest:

CASE 2.—History.—F. R., a white girl aged 14, admitted Nov. 21, 1937 (figs. 2 and 3), in October 1936 had gradually

11. Butler, A. M.: Chronic Pyelonephritis and Arterial Hypertension, *J. Clin. Investigation* **16**: 899 (Nov.) 1937.
12. Barney, J. D., and Suby, H. I.: Unilateral Renal Disease with Hypertension, *New England J. Med.* **220**: 744 (May 4) 1939. Barker, N. W., and Walters, W. L.: Hypertension Associated with Unilateral Nephritis: Treatment by Nephrectomy, *Mayo Clin. J.* **13**: 118 (Feb. 23) 1938.
13. Longcope, W. T.: Infected Unilateral Lesion, *Mayo Clin. J.* **31**: 299, 1938.
14. Longcope, W. T.: Destructive Lesion of the Kidney, *Challenge to Urology, J. Urol.* **42**: 957 (Dec.) 1939.

8. Hinman, Frank: The Pathogenesis of Hydronephrosis, *Surg., Gynec. & Obst.* **58**: 356-376 (Feb., no. 2 A) 1934.  
9. Nesbit, R. M., and Ratliff, R. K.: Hypertension Associated with Unilateral Nephropathy, *J. Urol.* **43**: 427 (March) 1940.  
10. Longcope, W. T.: Chronic Bilateral Pyelonephritis: Its Origin and Its Association with Hypertension, *Ann. Int. Med.* **11**: 149 (July) 1937.

increasing productive cough, dyspnea with exertion, orthopnea, palpitation and tachycardia; also associated intermittent episodes of precordial oppression which became more marked one week previous to admission. There were also occasional mild headaches but no visual changes.

**Examination.**—The patient was well developed and nourished and had moderate respiratory difficulty; her temperature was



Fig. 5 (case 3).—Retrograde pyelogram showing a gross destructive process of right kidney suggestive of tuberculosis. Left kidney is normal with hypertrophy.

100 F., respiratory rate 38 and pulse rate 120; the ocular fundi showed moderate venous engorgement. Cardiac examination revealed a visible apex impulse over the entire precordium and a lower border of cardiac dullness in the sixth interspace 10 cm. from the midsternal line. The aortic and pulmonic second sounds were greatly accentuated; the blood pressure was 210 systolic and 150 diastolic. Intravenous pyelograms Dec. 31, 1936, showed a large normal right kidney; the left was not visible.

**Laboratory Findings.**—The blood Kahn reaction was negative. The blood showed red blood cells 5,100,000, hemoglobin 90 per cent (Sahli) and white blood cells 13,000. The urine (Dec. 8, 1936) showed albumin 2 plus, increasing to 4, and a variable number of casts, loaded with white blood cells and bacilli. Urea clearance was 124 per cent. An electrocardiogram showed sinus tachycardia and myocardial changes.

**Course in Hospital.**—The patient was given sedatives and digitalis. Other symptomatic and specific therapy instituted gave no relief from cardiac symptoms, nausea and vomiting, edema, infection of the urinary tract or terminal pneumonia. Respirations ceased at the end of the third month of hospitalization. The blood pressure had gradually decreased through the last illness and was 70 systolic and 50 diastolic three days before death.

**Autopsy.**—Postmortem examination revealed advanced, practically complete pyohydronephrotic atrophy and fibrosis of the left kidney; vascular thickening in the left kidney; cardiac insufficiency, and hypertrophy and dilatation of the right and left ventricles. The right kidney showed some compensatory hypertrophy, with small arteriosclerotic foci of fibrosis and atrophy beneath the capsule. The kidney was essentially normal, as were other viscera of the body.

In this case death occurred as a result of hypertension with cardiac decompensation. One may reasonably infer that chronic unilateral pyelonephritis was the cause of this child's hypertension. Microscopic examination of the various tissues did not disclose any of the changes of necrotizing arteriolitis ordinarily associated with malignant hypertension. It is noteworthy that on admis-

sion the urea clearance test was normal. Considering the relatively normal condition of other organs of the body as seen at autopsy, including the opposite kidney, we feel that an early nephrectomy might have saved the life of this patient.

**CASE 3.—History.**—A. B., a white man aged 35, admitted in November 1938 (figs. 4 and 5), had had repeated attacks of gross hematuria with onset five months before. For as long as ten years he had recurring aching pain in the right flank. There was a known blood pressure of 185 systolic and 110 diastolic for over a year.

**Examination.**—The blood pressure was 200 systolic and 110 diastolic. Ophthalmoscopic examination revealed old hemorrhagic and exudative retinitis in each eye and mild hypertensive retinitis in each eye. Blood studies showed the blood to be normal. The blood Kahn reaction was negative. The nonprotein nitrogen level was 27.6 mg. per hundred cubic centimeters; urea clearance was 63 and 58 per cent. The urine was normal, with the exception of a few red blood cells; a culture of it was positive for *Staphylococcus albus*. In a split function test there was appearance of dye from the right kidney in five minutes and from the left in one minute. Pyelograms showed the right kidney to have advanced changes of chronic infection and the left to be normal.

**Operation.**—Excision of the right kidney was performed Nov. 3, 1938. A small, contracted and rather cystic-appearing kidney was removed.

**Pathology.**—The excised kidney measured 7 by 3 by 3 cm. The cut surface showed marked dilatation of the pelvis and calices with atrophy of the parenchyma. Microscopic study revealed inflammatory infiltrations beneath the mucosa, marked sclerosis of arterioles and arteriosclerotic nephropathy with advanced pyohydronephrotic atrophy.

**Result.**—The blood pressure gradually fell to 140 systolic and 90 diastolic on discharge from the hospital. Eight months postoperatively it was 140 systolic and 80 diastolic, and thirteen months postoperatively, 130 systolic and 86 diastolic, the patient

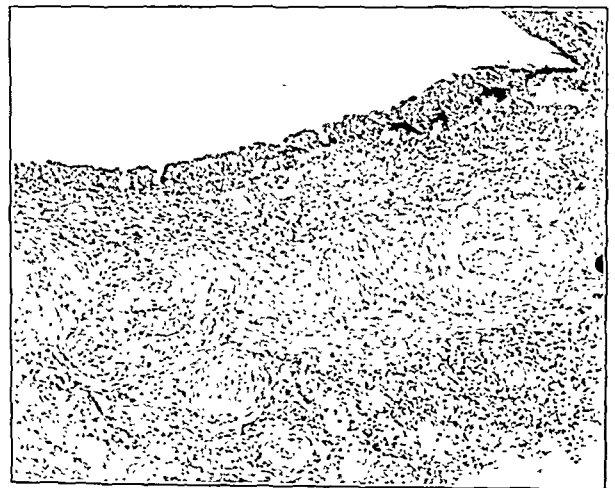


Fig. 6 (case 3).—Section showing marked sclerosis of arteries and inflammatory infiltration beneath pelvic mucosa.

working daily as a laborer. A urea clearance test showed the clearance to be 44 and 46 per cent. Changes in the eyegrounds were the same as they had been preoperatively. Sixteen months postoperatively the blood pressure was 145 systolic and 90 diastolic.

In this case the removal of an advanced unilaterally pyelonephritic kidney has resulted in marked improvement of the patient's hypertension. Vascular changes elsewhere in the body as demonstrated by the eyegrounds may have resulted from the hypertension. A regression of these secondary vascular changes is problematic.

Of the 10 patients submitted to nephrectomy for advanced inflammatory lesions of one kidney associated with hypertension, 6 have shown marked and lasting improvement in symptoms as well as a persisting lowered blood pressure. Some of these patients have shown a normal total renal function as demonstrated by the

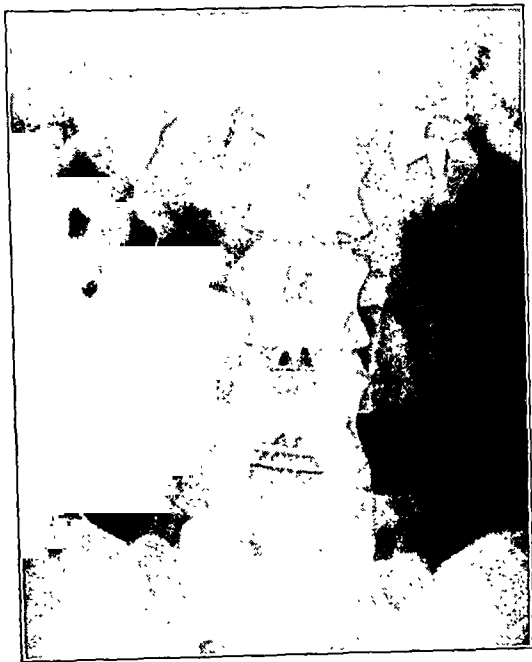


Fig. 7 (case 4).—Retrograde pyelogram showing a small contracted left kidney with a deformity of the pelvis characteristic of pyelonephritis. The right kidney is normal with moderate hypertrophy.

phenolsulfonphthalein, the nonprotein nitrogen and the urea clearance tests. Some have shown moderate impairment of function as determined by the phenolsulfonphthalein and urea clearance tests. Improved tests of renal function such as the inulin clearance and diodrast clearance tests may be of value in the future in determining the patients most suitable for operation and in establishing some clue as to prognosis.

**CASE 4.—History.**—E. B., a white woman aged 40, admitted in May 1939 (figs. 6 and 7), had had hypertension since toxemia of pregnancy eight years before, but no hypertensive symptoms until the onset of a convulsion in August 1938. Recently she had experienced some blurring of vision but no urologic symptoms. She had had scarlet fever in childhood.

**Examination.**—The blood pressure was 200 systolic and 120 diastolic. The patient had hypertensive retinitis; she also had active chorioretinitis in the left eye and tenderness in the left costovertebral region. The urine was normal. A culture of renal specimens was negative for bacteria. The Kahn reaction was negative. Two urea tests showed the clearance to be 41 per cent and 40 per cent respectively. The nonprotein nitrogen level was 28 mg. per hundred cubic centimeters. A split kidney function (phenolsulfonphthalein) test resulted as follows: Appearance time of dye from the right kidney was immediate, and from the left, ten minutes. The output of the right kidney was 5 per cent in ten minutes, and that of the left, 2.5 per cent. The blood showed hemoglobin 88 per cent, white blood cells 5,200 and red blood cells 5,050,000. Pyelograms showed the right kidney to be normal and the left small, pyelonephritic and contracted.

**Treatment.**—The left kidney was excised May 29, 1939.

**Pathology.**—The kidney measured 7 by 3.5 by 2.5 cm. and weighed 25 Gm. Advanced arteriosclerotic nephropathy was present, and primary contraction.

**Result.**—Postoperative blood pressure varied between 120 systolic and 70 diastolic to 165 systolic and 110 diastolic. Two months postoperatively there was subjective improvement; no convulsions occurred. The blood pressure was 200 systolic and 125 diastolic.

Twelve months postoperatively there was a return of all symptoms, including headaches, convulsions, weakness and blurring of vision. The blood pressure was 225 systolic and 125 diastolic.

The patient just mentioned and three others have been operated on for what appeared to be unilateral inflammatory renal lesions with associated hypertension and have been unimproved by nephrectomy. Studies of renal function carried out in these unsuccessful cases have not importantly differed from the results of the same studies carried out in the more successful cases. Two of the four failures have occurred in female patients who have dated their hypertension to toxemias of pregnancy seven or eight years previously. Perhaps bilateral vascular changes occurred in these 2 patients at the time of their toxemias.

Microscopic examination of the material obtained in 10 cases reveals the constant occurrence of vascular thickening. Whether this vascular change resulting from infection within the kidney has contributed to the production of hypertension is not known. Certainly many patients showing equal amounts of vascular sclerosis without associated hypertension have been observed both by us and by others. Perhaps perirenal fibrosis so commonly seen in these contracted kidneys has prevented an adequate collateral circulation and has been a contributing factor in the production of renal ischemia.

#### SUMMARY AND CONCLUSIONS

Experimental evidence and clinical observations have shown that hypertension may result from pathologic conditions of the kidney which may be bilateral or unilateral.

Three different types of unilateral renal lesion are most commonly associated with hypertension: (1) those

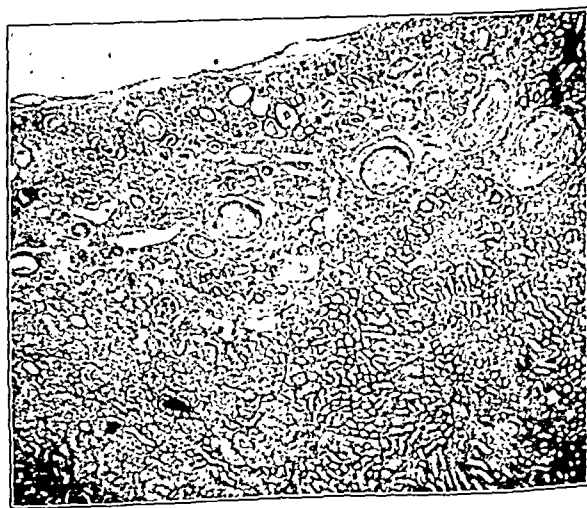


Fig. 8 (case 4).—Section showing marked sclerosis of arteries.

produced by gross vascular occlusion of the renal arteries including trauma to the kidney, (2) the obstructive uropathies and (3) chronic inflammatory lesions. Since chronic infection appears to be the most important single etiologic factor, it would appear that the best treatment of this type of hypertension is prophylactic. In this regard the value of modern chemotherapeutic



methods for prevention of chronic infections of the urinary tract cannot be overemphasized.

Hypertensive patients should be submitted to complete urologic study as a part of the routine examination even in the absence of a history of renal disorders or urinary findings suggesting disease of the urinary tract.

The rational treatment of the hypertensive patient with unilateral nephropathy is removal of the diseased kidney, provided the function of the opposite kidney is not importantly reduced. With this restriction, a reasonable expectancy of improvement or cure can be hoped for in the majority of cases.

#### ABSTRACT OF DISCUSSION

DR. E. GRANVILLE CRABTREE, Boston: We are participating in a magnificent effort to obtain a sound perspective on ischemic hypertension. Investigative work has already established the entity as a real thing, as the cases of Drs. Nesbit and Ratliff have shown, but it is still confused by a multiplicity of interpretations. Most clinics cannot make use of their vast statistics on nephrectomized patients because of insufficient data but must collect from current cases now studied from the blood pressure angle as well as urologically. From three such studies which have been made by me and my associates I doubt that, except as terminal conditions, the number of hypertensive patients found will be as high as we were at first led to suspect, and yet I want to emphasize that intensive search for these cases, such as Drs. Nesbit and Ratliff have made, is most important in the setup. Let me call attention to the nature of vascular damage in acute pyelonephritis. Dr. Prien and I showed in a recent article in the *Journal of Urology* that extensive injury to the vessels in the acute lesion is easily found. Also let me mention that Weiss has shown that vascular nephritis may appear in such cases within six months. Longcope has held that pyelonephritis becomes hypertensive with renal failure, and Butler has found, as Drs. Nesbit and Ratliff have shown, that in children function need not be lost. This is confusing but indicates the importance of the initial lesion. The three surveys which I have shown that in pregnancy with pyelonephritis unassociated with toxemia, out of 72 cases, after five to eighteen years after the injury, 8 were hypertensive, with 150 systolic and 90 diastolic as the upper limit of normal blood pressure. Chaset and I have reported the fact which Drs. Nesbit and Ratliff have referred to, that extensive vascular changes could exist without hypertension. Braasch's paper yesterday and this paper today show that these cases are frequent enough to look for and to try to correct. We are now entering on the third phase. The work of Page, which followed that of Goldblatt, and the work of Harrison, Grollman, Williams, and Page and Helmer, show the importance of physiology in contrast to pathology. Histologically these extensive changes may be found without the hypertension. Page's work tends to show that an adjustment is made to the secretion of renin, similar to that noted in the disturbances of the endocrine glands. Charlotte Crabtree has shown glomerular change in the cortex of the kidney which takes place normally in mice at puberty, and in castrates, with estrogen or testosterone injections.

DR. GEORGE WINTHROP FISH, New York: During the past three years Schroeder and I have studied and nephrectomized a group of hypertensive patients from 16 to 32 years of age with unilateral renal lesions, at least as far as we were able to establish such a diagnosis by intravenous and retrograde urography, separate phenol red and urea clearance determinations of the kidneys, and cultures of separated ureteral specimens. Even with all these tests the presence of bilateral lesions is not always ruled out. Perhaps most important of all, the time of the onset of hypertension in these cases was known and those whose hypertension did not extend beyond two years responded most favorably. These cases were reported in the May issue of the *American Journal of the Medical Sciences*. Drs. Nesbit and Ratliff mentioned failure in cases in which hypertension was known to have been present for from six to eight years, and Dr. Crabtree has reported a case in which hypertension returned

ten years after nephrectomy. The difficulty of establishing the diagnosis of unilateral kidney involvements, the uselessness of biopsy in the cases, and a striking example of normally functioning kidneys in a far advanced case of hypertension are well shown in one of our recent cases: A white man aged 40 had a stone removed from the right kidney through a pyelotomy incision in February 1937. The blood pressure was 130 systolic and 90 diastolic. In August 1937 the blood pressure was 148 systolic and 100 diastolic. Two attacks occurred of pyelitis on the right side between that date and April 1939. The blood pressure was 165 systolic and 120 diastolic at that time. The patient was first seen by me in October 1939 with the blood pressure ranging from 212 systolic and 140 diastolic to 154 systolic and 100 diastolic. The symptoms were headaches and lassitude. The problem here calls for the early diagnosis and the cooperation of all physicians and surgeons in obtaining complete urologic studies in every case of hypertension. Nephrectomy may prove of benefit but, it seems, only in patients in whom the existence of hypertension is of short duration and in whom arteriolar sclerosis of the other kidney is not advanced. Its use is probably limited, therefore, to a small number of hypertensive patients, and they remain potentially hypertensive. My hope is that before long a substance which will inactivate pressor substances and perform a chemical sympathectomy on these diseased kidneys will appear, and I believe it will.

DR. HENRY A. SCHROEDER, New York: Drs. Nesbit and Ratliff have made a valuable contribution to the knowledge of arterial hypertension associated with organic renal disease. Steele's and my series contain 35 per cent of renal diseases. It is necessary to realize that cases such as these are not a new development. In 1694 Marcellus Malpighi died of such an ailment: unilateral hydronephrosis and calculi; apoplexy, and left ventricular hypertrophy. Richard Bright in 1840 described four cases in which apparently this same condition existed, that is left ventricular hypertrophy, a recognized index of hypertension, and unilateral renal disease. After a lapse of a hundred years it is being again recognized that cases of arterial hypertension exist in which various kinds of renal diseases seem to play part of the causative role. Many, including myself, have been able to duplicate in animals, especially rats, some of these renal lesions and to produce hypertension, thereby establishing an experimental analogue for such cases. The significance of infection is still undetermined. The presence of arteriolar lesions, to which these authors have drawn attention, is most important. If the work of Wilson and Byrom is right, one is forced to the conclusion that vascular disease in the remainder of the body, including the unaffected kidney, is the result and, therefore, secondary to the existence of hypertension. It naturally follows that hypertension initiated by a unilateral renal disorder may be maintained, after the affected kidney is removed, by the secondary vascular disease in the other kidney, as was said, if this disease has progressed to an irreversible degree; if it has not, hypertension might well, for a temporary period, regress. One question remains to be answered, and the answer may contain the essence of the etiology of hypertension. Why do some persons with certain renal diseases develop hypertension while others with the same diseases do not? It appears that there are two factors at work in this type of case, a constitutional, perhaps hereditary, one and a renal one. Removal of the renal factor may result in regression, although I believe that these patients are still potentially hypertensive. Nephrectomy for hypertension seems to be a valuable palliative for a small group of cases in which the hypertension is of short duration, in which the arteriolar sclerosis of the other kidney is reversible, and in which the renal disease is confined to one kidney.

DR. REED M. NESBIT, Ann Arbor, Mich.: At the University Hospital one sees a large number of patients with hypertension referred from the medical and neurosurgical departments. This has been especially true in recent months because of increased recognition of the possibility of hypertension's being associated with renal infection even in the absence of urologic symptoms. Although the incidence of these cases is low as shown by the daily study of hypertensive cases in the clinic and reviews of nephrectomized patients, recognition of the syndrome does increase the number of both diagnoses and operations.

## BLASTOMYCOSIS AND THE BLASTOMYCOSIS-LIKE INFECTIONS

LESLIE M. SMITH, M.D.  
EL PASO, TEXAS

The clinical entity known since 1894 as Gilchrist's disease or American blastomycosis has usually been thought of as a mycologic entity as well. The subject has been complicated, however, by the incrimination of a number of different fungi as the causes of quite

histologic sections of most of the others and review of the literature of the entire group. The point of view is that of the clinician rather than that of the professional mycologist, and many of the finer details of mycology are omitted.

The more thorough the mycologic studies become the more different the fungi are found causing the disease pictures which fit into this group. In view of the different courses and prognoses of these diseases the importance of identification of the organism in each case is at once apparent. Clinical characteristics,

although suggestive, are usually not sufficient for accurate diagnosis. The appearance of the organism in the tissue is often not sufficiently characteristic for identification. Thorough mycologic studies are likely to yield information of prognostic and therapeutic importance.

Certain of the blastomycosis-like

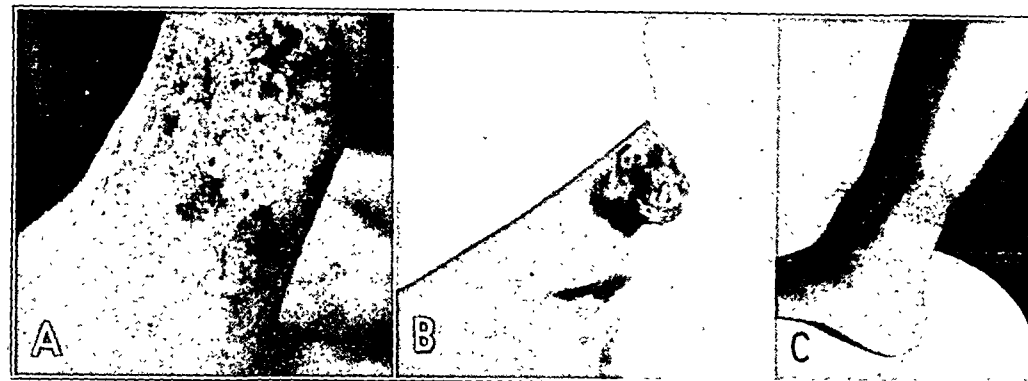


Fig. 1.—Three mycoses which present miliary abscesses and a verrucous surface: A, blastomycosis of Gilchrist; B, superficial type of coccidioidal granuloma; C, deep moniliasis.

similar lesions. It seems best, as Benham<sup>1</sup> has suggested, to reserve the name blastomycosis for lesions caused by the species of fungus described by Gilchrist and named *Blastomyces dermatitidis* and to apply appropriate names to the other somewhat similar diseases caused by other species of fungi. The latter may be collectively designated as the blastomycosis-like infections. This term will be applied here to the mycotic granulomas in which yeastlike cells are found, whether or not they are characterized by budding.

diseases may be suspected from their geographic origin, although this is of diminishing importance since more and more cases are being observed in geographic areas in which they have not hitherto been known to exist.

Others are suspected from their more or less characteristic clinical features, their minute structure and the type of parasitic cell found. A verrucous surface and miliary abscesses have usually been considered characteristic of Gilchrist's disease, but these features may occur in the superficial type of coccidioidal granuloma,

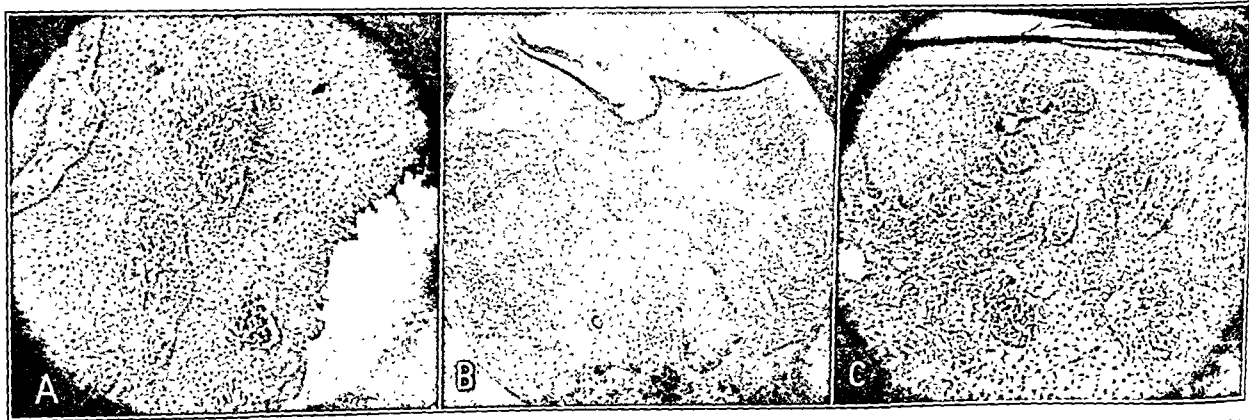


Fig. 2.—Verrucous surface and intra-epidermal abscesses in three different mycoses: A, blastomycosis of Gilchrist; B, superficial type of coccidioidal granuloma; C, deep moniliasis (*Monilia nigra*).

My purpose in this paper is to present these more or less similar diseases as a group and to emphasize their similarity and the importance of their differentiation in practice. This work is based on personal experience with several members of the group, study of cultures and

and Smith and Lewis<sup>2</sup> have reported a blastomycosis-like lesion of the leg, apparently due to *Monilia nigra*, with the same characteristics. The extreme adenopathy of paracoccidioidal granuloma suggesting Hodgkin's disease, the marked fungating character of chromomycosis, the polypoid tumors of rhinosporidiosis, the gelatinous contents of torular abscesses and the kala-azar-like syndrome of histoplasmosis are distinguishing clinical features.

2. Smith, L. M., and Lewis, G. M.: Deep Mycotic Infection Caused by *Monilia Nigra*, *South. M. J.* 29:1067 (Nov.) 1936.

Read before the Section on Dermatology and Syphilology at the Ninety-First Annual Session of the American Medical Association, New York, June 14, 1940.

Drs. George M. Lewis, Fred Weidman, H. P. Jacobson, Morris Moore, George Caldwell, Sidney Wilson, Ethel Rockwood and C. D. Stewart, placed cultures, microscopic slides and other material at my disposal for assistance in this study.

1. Benham, Rhoda W.: The Fungi of Blastomycosis and Coccidioidal Granuloma, *Arch. Dermat. & Syph.* 30:385 (Sept.) 1934.

As to the parasitic cells, those of Gilchrist's disease and coccidioidal granuloma may be indistinguishable at certain stages. Budding cells are not always found in Gilchrist's disease without very thorough search, and endosporulating cells are absent from many sections of coccidioidomycosis. If the multiple protoplasmic buds of paracoccidioidal granuloma are not demonstrable, the cells are much like those of coccidioidal granuloma and blastomycosis of Gilchrist. The round,

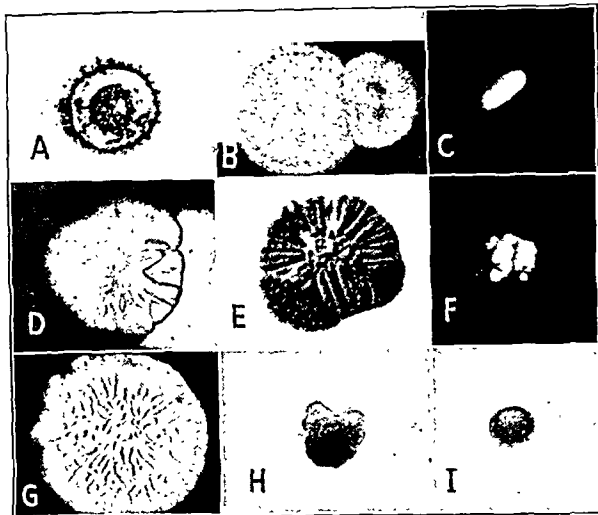


Fig. 3.—Cultures of A, *Blastomyces dermatitidis*, C, *Coccidioides immitis*, D, *Paracoccidioides brasiliensis*, E, *Torula histolytica*, F, *Monilia albicans*, G, *Paracoccidioides cerebriformis*, H, *Sporotrichum schenckii*, I, *Hormodendrum* (compactum?) and I, *Phialophora verrucosa*.

dark, thick-walled, nonbudding cells of chromomycosis are characterized by grouping and transverse fission. Budding yeastlike cells occur in several members of the group. Rockwood<sup>3</sup> states that in the case of deep moniliasis reported by Greenwood and Rockwood<sup>4</sup> the budding cells were not encapsulated. Hyphae may also

TABLE 1.—Geographic Distribution of Blastomycosis and Blastomycosis-like Infections (from Reported Cases)

Blastomycosis.....	North America, especially central states of United States
Coccidioidomycosis.....	United States, especially the valley of California; few cases in South America
Paracoccidioidal granuloma	South and Central America
Chromomycosis.....	South America, West Indies, United States, Russia, Japan, Africa
Moniliasis (deep).....	United States
Torulosis.....	Europe, United States
Sporotrichosis.....	Throughout the world
Scopulariopsis (deep).....	United States (Colorado), Europe, Africa
Rhinoporioidosis.....	India, Ceylon, Italy, North and South America
Histoplasmosis.....	United States, Central America, Isthmus of Panama

be present in moniliasis. The encapsulated budding cells of torulosis, although smaller, may be mistaken for young forms of *Blastomyces*. The minute, non-budding, round bodies, as described by Markley, Philpott and Weidman,<sup>5</sup> should lead one to suspect scopulariopsis. I have studied sections from Caldwell and Roberts<sup>6</sup> case of rhinoporioidosis, and I do not believe that the cystlike sporangia of that disease could

be confused with any other condition. The many small conidia found in histoplasmosis within the endothelial and giant cells are characteristic. The round and oval conidia of *Sporotrichum* are difficult to identify, although Lawless<sup>7</sup> gives variation in size and a tendency to grouping as characteristic features of these cells.

#### THE ORGANISMS

In some of the diseases of the blastomycosis-like group a single species of fungus is responsible almost invariably for the condition; in others there is a multiplicity of organisms capable of causing identical lesions. Unfortunately there is not a uniform nomenclature among mycologists, and fungi given different names and classifications have been found to be the same or closely related organisms, so that the multiplicity is not as great as at first appears. A uniform nomenclature would eliminate much of the confusion that now exists. A number of supposedly different strains have been described as the cause of certain cases of Gilchrist's disease. Benham<sup>1</sup> studied five such strains and found them sufficiently similar to classify them all in the species described by Gilchrist.<sup>8</sup> The organism of coccidioidomycosis, originally thought to be protozoan, was shown by Ophuls and Moffitt<sup>9</sup> to be a fungus, and the name *Coccidioides immitis* was applied to it by Rixford and Gilchrist. So-called South American blastomycosis or paracoccidioidal granuloma is caused by several species of *Paracoccidioides*, most often *Paracoccidioides*

	TISSUE	CULTURE
BLASTOMYCES DERMATITIDIS		
COCCIDIOIDES IMMITIS		
PARACOCIDIOIDES BRASILIENSIS		
HORMODENDRUM PEDROSOI		
PHIALOPHORA VERRUCOSA		
MONILIA ALBICANS		
TORULA HISTOLYTICA		
SPOROTRICHUM SCHENCKII		
SCOPULARIOPSIS BREVICULIS		
RHINOSPORIDIUM SEEBERI		
HISTOPLASMA CAPSULATUM		

Fig. 4.—Diagrammatic representation of organisms in tissue and culture.

*brasiliensis*. Moore<sup>10</sup> states that the generalized form of the disease is due to *Paracoccidioides brasiliensis* and *P. tenuis*, and the localized form involving the buccal mucosa to *P. cerebriformis*.

3. Rockwood, Ethel M.: Personal communication to the author.

4. Rockwood, Ethel M., and Greenwood, A. M.: Monilial Infection of the Skin—Report of a Fatal Case, *Arch. Dermat. & Syph.* 29: 574 (April) 1934.

5. Markley, A. J.; Philpott, O. S., and Weidman, F. D.: Deep Scapulariopsis of Ulcerating Granuloma Type Confirmed by Culture and Animal Inoculation, *Arch. Dermat. & Syph.* 33: 627 (April) 1933.

6. Caldwell, G. T., and Roberts, J. D.: Rhinoporioidosis in the United States, *J. A. M. A.* 110: 1641 (May 14) 1938.

7. Lawless, K. L.: Diagnosis of Sporotrichosis, *Arch. Dermat. & Syph.* 22: 381 (Sept.) 1930.

8. Gilchrist, T. C.: Case of Blastomycetic Dermatitis in Man, *Johns Hopkins Hosp. Rep.* 1: 269, 1896.

9. Ophuls, William, and Moffitt, H. C.: *Philadelphia M. J.* 5: 1471, 1900.

10. Moore, Morris: Blastomycosis, Coccidioidal Granuloma and Paracoccidioidal Granuloma, *Arch. Dermat. & Syph.* 38: 163 (Aug.) 1938.

In cases of dermatitis verrucosa or chromomycosis several organisms have been described. Lewis<sup>11</sup> quotes Carrión as stating that any of three fungi may be responsible: *Hormodendrum pedrosoi*, *Hormodendrum compactum* or *Phialophora verrucosa*, and he believes that they are generically related. Moore and Almeida,<sup>12</sup> who have studied the disease in South America, recognize as causative *Acrotheca*, *Phialophora*, *Hormodendrum*, and possibly *Trichosporium*. The species of *Monilia* usually pathogenic is *Monilia albicans*, although occasionally other species are apparently capable of causing disease. *Torula histolytica*, or *Cryptococcus hominis*, is the organism of so-called European blastomycosis. *Sporotrichum schenckii* is the predominating cause of sporotrichosis in this country, although other species are sometimes pathogenic. Markley, Philpott and Weidman described a deep mycosis due to *Scopulariopsis brevicaulis*, the first such case in the American literature. *Rhinosporidium seeberi*, the etiologic agent of rhinosporidiosis, and *Histoplasma capsulatum*, of histo-

diagnosis and are worthy of further study. The reactions are of the tuberculin type, appearing in from twenty-four to forty-eight hours. A positive reaction to sporotrichin almost always occurs in sporotrichosis, although the reaction occasionally occurs in other mycoses as well. A negative reaction, according to Sulzberger,<sup>13</sup> speaks with a degree of certainty for the absence of sporotrichosis. In cases of coccidioidomycosis, Jacobson<sup>14</sup> and many others have found the cutaneous test with coccidioidin to be specific and of definite diagnostic value. On account of the many opportunities for sensitization to *Monilia* through oral, intestinal and intertriginous lesions, a positive reaction with oidiomycin is so common as to be of no aid in diagnosis. I have not found in the literature a satisfactory evaluation of the cutaneous reaction in Gilchrist's disease, torulosis or the rarer members of the blastomycosis-like group. With the exception of coccidioidomycosis in California, none of these diseases have occurred in large numbers in any locality. It is therefore difficult for any observer to compile enough case reports from which to evaluate these reactions. One can hope to do this only by combining the experiences of many observers. One is justified, therefore, in adding one's personal experience, even though it is not extensive.

It is now my practice to test patients with deep mycoses and suspected mycoses by means of several fungous antigens prepared from cultures in dextrose broth. In this way, although the reactions may not be absolutely specific, a comparative study of the degree of reaction to the several similarly prepared antigens should be of value. At present routine intradermal tests are being performed with coccidioidin, blastomycin and sporotrichin prepared in my office and with oidiomycin obtained from a biological manufacturer. Oidiomycin has been of no value but rather has served to obscure the issue because of the frequent positive reactions. Five cases of coccidioidal granuloma tested all showed a positive reaction to coccidioidin and no reaction to blastomycin. In one of these cases a test with sporotrichin gave negative results. One case of moniliasis showed a strong and persistent reaction to an autogenous antigen (*Monilia nigra*), no reaction to coccidioidin and a very slight and short-lived reaction to blastomycin. In 1 case of Gilchrist's disease only a moderately positive reaction was obtained with blastomycin and no reaction with coccidioidin or sporotrichin. One case of sporotrichosis showed repeated positive reactions to tests with sporotrichin and showed no reaction to coccidioidin or blastomycin. Most of these cases showed a positive reaction to oidiomycin. Experience indicates that persons with these diseases retain their capacity to react to their specific antigens for months or years after all clinical evidence of the disease has disappeared.

Judging from the experience of others, and from my own, it appears that coccidioidin, sporotrichin and probably blastomycin are of value in confirming or denying the presence of the corresponding diseases. In my

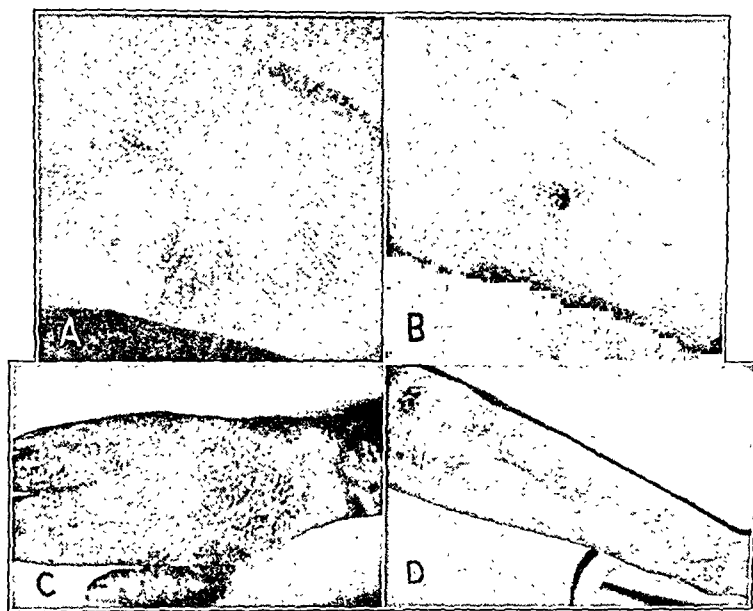


Fig. 5.—Four nonmycotic conditions which may closely simulate mycoses of the blastomycosis-like group: A, Ioderna, B, *Micrococcus myceticus* infection, C, tuberculosis verrucosa cutis, D, tertiary syphilis (simulating sporotrichosis).

plasmosis, are organisms of increasing clinical importance. Most of these organism are described in table 3.

#### IMMUNOLOGIC PHENOMENA

Various immunologic phenomena have been observed in several members of the blastomycosis-like group of diseases. The allergic eruptions usually referred to as "ids" have been seen associated with sporotrichosis, coccidioidomycosis and moniliasis. One would therefore expect to find them occasionally in other similar infections.

Positive complement fixation reactions have been obtained by various investigators in several of these mycoses, but the reactions are not sufficiently specific to be of diagnostic value. The same appears to be true of precipitation and agglutination reactions.

The local reactions to intracutaneous injections of specific fungous antigens appear to be of some aid in

11. Lewis, G. M., and Hopper, Mary E.: *An Introduction to Medical Mycology*, Chicago, Yearbook Publishers, 1939, p. 154.

12. Moore, Morris, and Almeida, F.: *Etiologic Agents of Chromomycosis of North and South America*, *Rev. di biol. e hyg.* 6:94 (Dec.) 1935.

13. Sulzberger, M. B.: *Dermatologic Allergy*, Springfield, Ill., Charles Thomas, Publisher, 1940, p. 320.

14. Jacobson, H. P.: *Fungous Diseases*, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

series the reaction to blastomycin was less definite than the others. A considerable number of control persons have been tested with these antigens and almost all have failed to react. Two persons have been tested, however, who gave positive reactions to several of the antigens and who had never had any evidence of any of these diseases. Both subjects were extremely sensitive to trichophytin. They were not sensitive to the ingredients of the broth from which the antigens were prepared or to the dilute phenol used as a preservative, and it is difficult to explain the positive reactions except on a basis of group fungous sensitivity.

many open sinuses there is so much pyogenic infection as to make the finding and isolation of fungi a difficult problem.

The so-called "pseudomycoses" may resemble the true mycoses. Indolent nodules, sinuses and ulcers caused by *Micrococcus myceticus* of Castellani<sup>15</sup> or *Bacillus typhosus*, and deep-seated, bruise-like nodules of *Bacillus pyocyaneus*, mentioned by Weidman,<sup>16</sup> belong to this group. I have seen 2 cases presenting deep infiltrations and sinuses due to *Micrococcus myceticus* which resembled sinuses of coccidioidal granuloma, although somewhat more acute in appearance.

TABLE 2.—Clinical Pictures of Blastomycosis and Blastomycosis-like Infections

Disease	Description	Prognosis as to Life
Blastomycosis.....	Infiltration with verrucous surface, milary abscesses, ulceration....	Good
Coccidioidomycosis.....	1. Acute pulmonary infection (valley fever)..... 2. Coccidioidal granuloma: Verrucous lesion with milary abscesses; subcutaneous abscesses and sinuses; involvement of bones, joints and viscera (except intestinal tract)	1. Good 2. High mortality
Paracoccidioidal granuloma	Furunculoid nodules beginning about the mouth; may be verrucous; extreme adenopathy resembling Hodgkin's disease; intestinal tract involved	Fatal
Chromomycosis.....	Elevated, verrucous, dark growths; mostly on legs.....	Good; does not usually become systemic
Monilliasis (deep).....	Subcutaneous abscesses, ulcers, hyperkeratotic infiltration.....	Serious if systemic
Torulosis.....	Acanthiform pustules, granuloma-like ulcers, deep abscesses, subcutaneous nodules without ulceration, involvement of central nervous system	Grave except in cases of localized involvement
Sporotrichosis.....	Primary ulceration and nodules along lymphatics, disseminated nodules and ulcerations; occasionally visceral involvement	Usually good
Scopulariopsis (deep) ....	Painful nodules .....	Good
Rhinosporidiosis.....	Pinkish polypoid masses beginning on nasal septum; skin involved by transplantation	Prone to recur unless destruction is thorough
Histoplasmosis.....	Intermittent fever, splenohepatomegaly, anemia, leukopenia.....	Fatal

TABLE 3.—Description of Usual Organisms in Tissue and Culture

Disease	Organism	Appearance in Tissue	Appearance in Culture
Blastomycosis.....	<i>Blastomyces dermatitidis</i>	Rounded, encapsulated cells, some with buds	Amount mycelium varies with medium; grouped, large round chlamydospores characteristic; mycelium septate; raquets
Coccidioidomycosis.....	<i>Coccidioides immitis</i>	Rounded, encapsulated cells, some with endospores	Coarse, septate mycelium, raquets, arthrospores and chlamydospores
Paracoccidioidal granuloma	<i>Paracoccidioides brasiliensis</i>	Rounded, encapsulated cells without distinct endospores, multiple small protoplasmic buds	Asci with spores inside and protruding; septate mycelium and chlamydospores
Chromomycosis.....	1. <i>Phialophora verrucosa</i> 2. <i>Hormodendrum pedrosoli</i>	1 and 2. Thick-walled, dark cells, some showing transverse fission; no buds	1. Septate mycelium, flask-shaped conidiophores; 2. Mycelium septate, conidiophores bearing branching chains of conidia
Monilliasis.....	<i>Monilla albicans</i>	Rounded, budding cells; hyphae may be present	Some mycelium, masses of conidia, chlamydospores; no asci
Torulosis.....	<i>Torula histolytica</i>	Large number rounded, encapsulated cells, some budding	Budding cells; no ascospores; no mycelium
Sporotrichosis.....	<i>Sporotrichum schenckii</i>	Small, round or elongated spores, difficult to demonstrate	Profuse, fine mycelium; pear-shaped, elongated spores in groups on short stalks
Scopulariopsis.....	<i>Scopulariopsis brevicaulis</i>	Minute, encapsulated cells, difficult to identify	Septate, seldom branching, mycelium bearing long chains of conidia
Rhinosporidiosis.....	<i>Rhinosporidium seebi</i>	Numerous, very large cystlike sporangia containing many spores	Not grown on artificial mediums
Histoplasmosis.....	<i>Histoplasma capsulatum</i>	Many very small cells with pale capsules, within endothelial and giant cells	Septate mycelium, conidia and chlamydospores; asci with ascospores and multiple tubercle-like buds

#### CONFUSION WITH NONMYCOTIC LESIONS

There are several nonmycotic conditions which are especially likely to mimic the diseases of this group of mycoses. A group of gummas extending in linear arrangement may closely simulate sporotrichosis. Ioderna and bromoderna at times give a picture similar to that of Gilchrist's disease, and when such a lesion occurs from iodide therapy in the course of blastomycosis or coccidioidal granuloma it is quite confusing. Tuberculosis verrucosa cutis usually has a dry verrucous surface, but in the presence of secondary pyogenic infection it somewhat resembles mycoses of this group. Sinuses extending to the surface from infections of bone and other deep structures are often difficult to differentiate from mycotic infection. In

#### PROGNOSIS

The prognoses of these diseases vary considerably. Blastomycosis of Gilchrist usually does not become systemic, although it occasionally does, with corresponding darkening of the outlook. A good many cases are responsive to iodides and roentgen therapy, although many cases are resistant to all known forms of therapy. With the acute pulmonary form of coccidioidomycosis the patient almost always recovers, but in coccidioidal granuloma the response to treatment is usually poor and the eventual mortality high. Jacobson,<sup>17</sup> however,

15. Castellani, Aldo: Pseudomycosis Due to Coccus: *Micrococcus Myceticus*, Arch. Dermat. & Syph. 18: 857 (Dec.) 1928.

16. Weidman, F. D.: Cutaneous Torulosis, South. M. J. 26: 851 (Oct.) 1933.

17. Jacobson, H. P.: Immunotherapy for Coccidioidal Granuloma, Arch. Dermat. & Syph. 40: 521 (Oct.) 1939.

reported good results from intravenous injections of coccidioidin. Paracoccidioidal granuloma has the reputation of being a fatal disease. Chromomycosis, or chromoblastomycosis, usually remains localized, but Carrión<sup>18</sup> has reported a case presenting metastatic lesions. Whereas some of the American cases have responded to iodide therapy, Carrión's experience in Puerto Rico has been that they are difficult to cure. Moniliasis in systemic form offers a serious prognosis. Torulosis, since it usually sooner or later involves the central nervous system, is likely to be fatal. Sporotrichosis, if localized, usually responds to iodides; with deeper involvement the outcome is less certain. In the case of scopulariopsis referred to, cure was brought about by iodides. Lesions of rhinosporidiosis must be thoroughly destroyed; otherwise they are prone to recur. Histoplasmosis, as far as I am able to ascertain, always results in death.

#### SUMMARY AND CONCLUSIONS

The clinical characteristics of blastomycosis of Gilchrist and the group of other mycoses in which yeast-like bodies are found are often not sufficient for diagnosis. In some forms of the group the microscopic appearance of the organism may be characteristic and diagnostic but in most cases the study of cultures is necessary. An accurate mycologic diagnosis is important in view of the different prognoses and the varying degrees of therapeutic response of infections by these different fungi, and for the purpose of adding new members to the list of possible pathogens. Intracutaneous tests with fungous antigens offer some assistance in diagnosis but must not be considered absolutely specific.

931 First National Bank Building.

#### ABSTRACT OF DISCUSSION

DR. GEORGE M. LEWIS, New York: Medical teachers appreciate the value of comparative studies of similar disease processes to bring out the salient features common to all. Since these fungous diseases are of uncommon occurrence, one is well advised to have clear mental pictures of the disease processes. Dr. Smith's work demonstrates the value of practical mycologic investigation that can be carried out by the practicing physician. I am in favor of grouping diseases when it is possible and believe it is justifiable to overlook the finer differences in strains of pathogenic fungi in order to correlate the clinical with the mycologic. As Dr. Smith mentioned, pooling of experiences is really necessary with the rare mycoses, since no one observer can hope to have a sufficiently broad personal experience to be of decisive value. In a case of blastomycosis in New York, there was sensitivity to an autogenous vaccine made from *Blastomyces dermatitidis* and this was thought to be specific, as other antigens failed to elicit comparable reactions. Of other fungous vaccines used in diagnosis, I believe trichophytin to be of value particularly in a negative way and when used in connection with cultural studies. Dr. Smith's results with oidiomycin coincide with the results which my associates and I have published, namely that oidiomycin is of no use as a diagnostic aid, since reactions following its administration are too frequent when there is no clinical history or evidence of moniliasis. The test often gives a negative reaction when the patient has an obvious monilia infection. We believe the manufacturers of the commercial product oidiomycin should withdraw the vaccine from the market since it is not of any importance in diagnosis. Its only use in our hands is as a control. Coccidioidin appears to elicit specific reactions, but it may be of limited diagnostic value in communities where the disease is endemic. Farness and Woolley demonstrate this in the Scientific Exhibit, in which

they show that 90 per cent of school children in a district of California in which coccidioidomycosis is prevalent all gave a positive reaction to coccidioidin, showing that the test there would be entirely valueless. In New York State no case of coccidioidomycosis has yet been reported and in over three hundred tests with coccidioidin we failed to find a positive reactor.

DR. LESLIE M. SMITH, El Paso, Texas: I have had no experience with thymol, sulfanilamide or sulfapyridine in the treatment of these mycoses. I have tried almost every other recommended method of treatment, and with many disappointments. Colloidal copper, colloidal iodine, iodides and antimony and potassium tartrate have all been used in my work with the mycoses of this group with varying results. In coccidioidal granuloma I have tried coccidioidin without result, although I have not yet used it intravenously as recently recommended by Jacobson.

### DISEASES OF THE COMMON BILE DUCT AND THEIR RELATION TO THE GASTROINTESTINAL TRACT

WITH SPECIAL REFERENCE TO THE ROLE OF  
CHRONIC PANCREATITIS

MOSES BEHREND, M.D.

PHILADELPHIA

It is my purpose in this paper to review briefly some of the common disorders affecting the biliary tract and to call special attention to the importance of the role played by chronic pancreatitis.

According to Walters and Snell<sup>1</sup> two types of chronic pancreatitis are recognized, the interlobular type and the interacinar type. Both are characterized by an increase in fibrous tissue, but in the former the islands of Langerhans are spared, while in the latter they are not.

In my experience neither hyperglycemia nor insufficiency of pancreatic secretion (as evidenced by bulky and fatty stools) need be present in cases of chronic pancreatitis that may yet be sufficiently severe to produce symptoms of obstruction of the common duct.

#### SYMPTOMS

The commonest symptoms of disease of the common bile duct are pain, nausea, vomiting and eructations of gas. Collectively these phenomena are usually called "indigestion" or dyspepsia. Jaundice may be an early or a late sign of biliary obstruction. Chills and fever suggest that infection of the biliary tract is present. In obstruction of the common duct acholic stools, a positive van den Bergh reaction and elevation of the icterus index help to complete the picture. When obstruction is complete or practically complete urobilinogen is absent from the urine.

*Pain.*—The severity of pain in diseases of the common bile duct varies. It is located usually in the epigastric and hypochondriac regions. Pain may be referred to the back, shoulder, right iliac region and transversely across the umbilical line. The severity of the pain may sometimes aid in the diagnosis of the lesion causing obstruction to the common duct. It is severe when a stone is passing through the common duct, but the severest pain of all is that which accompanies obstruction

From the Services of the Jewish and Mount Sinai hospitals.  
Read before the Section on Gastro-Enterology and Proctology at the  
Ninety-First Annual Session of the American Medical Association, New  
York, June 14, 1940.

1. Walters, Waltman, and Snell, A. M.: Diseases of the Gallbladder  
and Bile Ducts, Philadelphia, W. B. Saunders Company, 1940.

18. Carrión, A. L.: Chromoblastomycosis in Puerto Rico, Puerto Rico  
J. Pub. Health & Trop. Med. 14:72 (Sept.) 1938



due to the swelling and inflammation caused by acute hemorrhagic pancreatitis. Pain due to chronic pancreatitis varies, depending on the extent and location of the disease. Attacks of colic attributable to pancreatitis are similar to those accompanying the passage of a stone in the common duct, but pain referred transversely across the umbilical line should make one suspicious of pancreatic disease.

**Nausea and Vomiting.**—Reflexly nausea and vomiting accompany all the disturbances referable to the bile passageways. These symptoms, together with pain, are universally present. Nausea and vomiting are rarely persistent, but the phenomena may be repeated if the cause is not removed. In patients who have been ill a long time from disease involving the bile passageways and the pancreas, nausea and vomiting may recur at intervals of a few hours or on several successive days. Fatty foods are usually not well tolerated by those having disease of the biliary tract.

**Jaundice.**—Jaundice due to stones in the common duct constitutes, in general, the painful type, while obstruction due to cancer of the head of the pancreas and the papilla of Vater usually gives rise to no pain. When accompanied by pain, jaundice is usually secondary to stones in the common duct, and when impaction of a stone at the papilla of Vater occurs jaundice is intense. On the other hand, I have seen the common duct practically packed with stones which did not cause jaundice. The so-called ball valve stone gives rise to alternating jaundice.



Fig. 1.—The gallbladder did not concentrate the dye. Chronic pancreatitis was revealed, for which cholecystogastrostomy was performed.

Jaundice may appear after attacks of pain due to chronic pancreatitis but is more often absent. The following case illustrates this:

A. B., a woman aged 49, was admitted to the Jewish Hospital March 6, 1940 complaining of frequent epigastric colic and pain in the right upper quadrant of the abdomen. Nausea and vomiting were present. She was operated on, and no stones were found in the gallbladder or common duct. The pancreas was exceedingly hard. Notwithstanding this hard

pancreas and its intermittent obstruction to the flow of bile there was absolutely no jaundice. A cholecystogastrostomy was performed. The immediate effect of the operation was magical. She has been entirely symptom free ever since.

Jaundice accompanying chronic pancreatitis gives a mild tinge of yellowishness, but that due to stones or

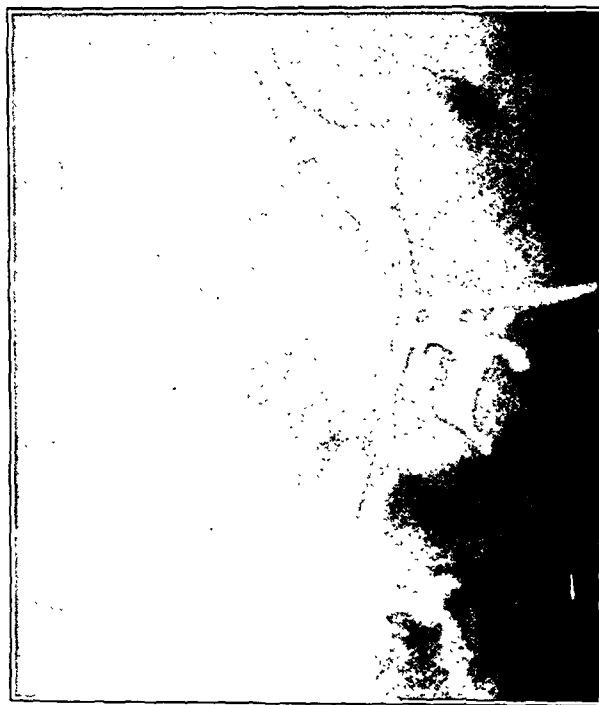


Fig. 2.—Cholelithogram illustrating T tube and patulous papilla of Vater. Lateral view.

a new growth at the head of the pancreas causes intense yellowish discoloration of the skin. The gallbladder is not distended in benign obstructions. The icterus index will be of some assistance because it is lower in patients suffering from chronic pancreatitis than in those in whom a complete obstruction is found.

Jaundice, if allowed to continue, produces degenerative changes in the entire organism, but especially in the heart, liver and blood. The surgeon should therefore operate to remedy the cause of obstruction within two to four weeks of its onset. Jaundice accompanied by fever, with or without chills, signifies infection of the biliary system and is usually due to suppurative cholangitis. Most commonly this occurs in the presence of stones of the common duct, but occasionally no stones are found. The following case illustrates suppurative cholangitis without stones:

F. M., a woman aged 33, was admitted to the Jewish Hospital March 28, 1940. Two days before admission she had had acute pain in the right upper quadrant of the abdomen with repeated episodes of vomiting. This attack occurred just before breakfast. Later in the day she became jaundiced and nausea continued. There was a history of a similar attack thirteen years previously. Fever and a slight chill accompanied the symptoms. She was operated on four days after admission. The common duct was opened, and a large amount of greenish purulent material exuded. No stones were found in the common duct but there were three large stones in the gallbladder. Cholecystectomy was performed, and a T tube was inserted in the common duct, which was irrigated daily with salt solution. Before the patient left the hospital a cholelithogram was made, and the papilla of Vater was found patulous. Iodized oil entered the duodenum.

Today physicians approach operations on the biliary passageways in the presence of jaundice with greater confidence as a result of the introduction of vitamin K. Ability to estimate the prothrombin time preoperatively and postoperatively has been a boon to the physician and the patient. The protection of the patient from

pancreas, but the gallbladder was small and shriveled and contained impacted stones. Nor should operation ever be deferred in cases in which jaundice is painless in the belief that such jaundice is always secondary to cancer.

*Chronic Pancreatitis and Obstruction of the Common Duct.*—It is sometimes practically impossible before operation to differentiate between the symptoms due to gallbladder disease, choledocholithiasis and chronic pancreatitis. At operation it requires considerable experience to differentiate between the grades of firmness and hardness of the pancreas. The pancreas should be palpated in all operations whenever such palpation is possible, so that one becomes familiar with its normal structure. Chronic pancreatitis must always be suspected when stones are absent from the gallbladder or common duct. Cholecystography may or may not be of positive value in such cases. The roentgenogram may be interpreted as showing evidence of gallbladder disease or even of cholelithiasis, but operation fails to confirm the findings (fig. 1). When the radiologist reports there is no disturbance of gallbladder function after the dye test, despite otherwise suggestive symptoms, chronic pancreatitis must be suspected. The only positive method of differentiation between stones in the common duct and chronic pancreatitis must be operation.

#### OPERATIONS

The operations performed on the common duct for benign conditions are those done for the removal of stones, obstruction due to stricture of the duct or

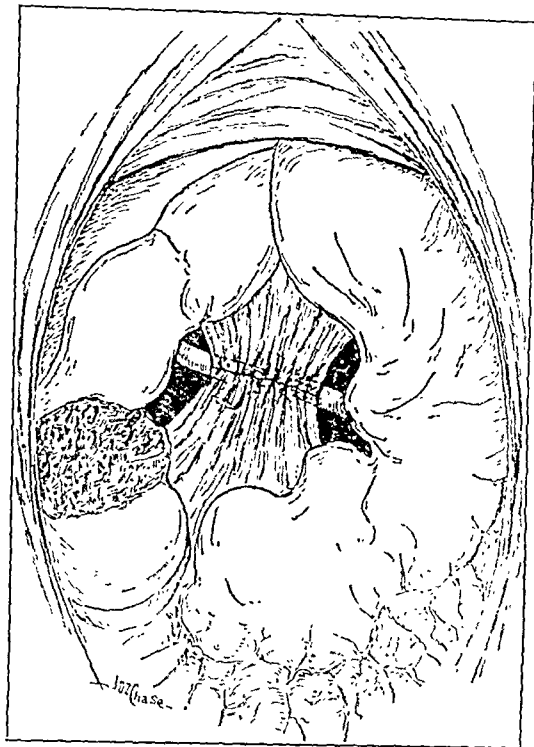


Fig. 3.—Immediate repair of common duct after an injury sustained in the performance of a cholecystectomy. Line of suture covered with omentum.

secondary hemorrhage after operations on the biliary passages is now practically assured by the administration of vitamin K and bile salts before and after operation. The recent introduction of a vitamin K product which may be used intravenously obviates the need for the coadministration of bile salts.

*Benign versus Malignant Obstruction.*—The main sign which aids in the differentiation of gallbladder disease from disease of the common duct is jaundice. Jaundice is nearly always present in obstruction of the common duct and absent in cholelithiasis unless (rarely) the pressure of stones in the gallbladder is great enough to cause blockage of bile passing through the common duct.

When a stone obstructs the cystic duct the gallbladder is enlarged and palpable. It may be felt as a pyriform mass in the right hypochondriac region. If a stone obstructs the common duct in the region of the papilla of Vater, the common duct is dilated, and if infection supervenes Charcot's fever manifests itself. When painless jaundice is present a malignant condition at the head of the pancreas or the papilla of Vater must be suspected. The gallbladder is greatly distended and can easily be felt in the right hypochondriac region. The physical signs will follow the well known law of Courvoisier. It does not always follow, however, that carcinoma of the papilla of Vater or of the head of the pancreas results in distention of the gallbladder. In several cases I have been prepared to perform the Whipple operation for carcinoma at the head of the



Fig. 4.—Anastomosis of common duct to duodenum. Same technic is used in performing choledochogastrostomy.

destruction of the duct by an error in technic in the removal of the gallbladder. Many unnecessary secondary operations can be avoided if the common duct is explored when the operation of cholecystectomy for cholelithiasis is performed. Of the 125 patients with obstruction of the common duct that I have operated on 20 per cent had choledocholithiasis.

Multiple operations on the common duct have been performed in several patients in whom there was a recurrence of stones. The following was a typical example:

B. S., a woman aged 55, was admitted to the Mount Sinai Hospital Nov. 17, 1938. Twelve years after cholecystectomy this patient returned with symptoms referable to gallstone colic with jaundice. She had recurrent attacks of pain. Operation was performed on the common duct. A ball valve stone was removed and a T tube was inserted. Ten days later the choledochogram showed that iodized poppyseed oil did not enter the duodenum. On Feb. 10, 1939 a second operation was performed, and at that time two soft stones were removed. The second choledochogram showed that the iodized oil entered the duodenum. The T tube was removed sixteen days after the second operation.

After all common duct operations for choledocholithiasis the T tube is used for external drainage. The T tube may remain from two weeks to six months or even a year, depending on the condition for which the patient was operated on. In cases of recurrent choledocholithiasis it is important that the T tube remain for months and be irrigated daily with salt solution. No T tube is removed unless a choledochogram has been made to determine the patulousness of the duct and the papilla of Vater (fig. 2).

Strictures of the common duct are due mainly to injury in the performance of the operation of cholecystectomy. In a few cases strictures are found without a history of previous operation. Such strictures probably occur on an inflammatory basis. Accidents to the common duct can be reduced to a minimum if proper consideration is given to anatomic relations in the region of the foramen of Winslow. Plastic operations on the duct are usually necessary to correct the results of such accidents. When transverse section of the common duct is detected at operation, immediate repair gives the best results (fig. 3). As an example of this the following case is cited:

R. H. B., a woman aged 34, was admitted to the Jewish Hospital July 1, 1937. There was pain in the right upper quadrant of the abdomen of six weeks' duration. She had had repeated attacks accompanied by nausea and vomiting. Mild diarrhea was present every day. Cholecystography revealed a diseased gallbladder. She came to operation on July 3, 1937, and stones were found in the gallbladder and in the common and hepatic ducts. During cholecystectomy the common duct was cut almost completely across. The error was discovered immediately. An end to end anastomosis was performed and a piece of omentum placed over the line of suture. The patient made an uneventful recovery, with the exception that a small secondary collection had to be opened fourteen days after operation. The patient is still well and has suffered absolutely no inconvenience as a result of the accident because an immediate repair was made.

*Operations for Chronic Pancreatitis.*—Years ago when a diagnosis of chronic pancreatitis was made external drainage operations were common. It required considerable effort on the part of some surgeons who were interested in surgery of the biliary tract to convince their colleagues that an anastomosis of the gallbladder to the stomach or duodenum was preferable to that of a cholecystostomy or choledochostomy (fig. 4).

Drainage of bile from the latter operations often continued for months as a result of unrelieved obstruction at the papilla of Vater due to pancreatitis. While anastomotic operations are more difficult to perform it was soon recognized that they were efficient and curative. Patients in whom recurrent colic without stones exists should never have the gallbladder removed.

As an illustration I report the following case:

L. S. L., a man aged 32, was admitted to the Jewish Hospital April 6, 1940. He stated that for six years he had had heartburn, palpitation and pain in the right upper quadrant of the abdomen. A roentgenogram taken in Germany six years before was interpreted as showing stones in the gallbladder. The patient arrived recently in this country and received continuous medical care without relief. He was operated on two days after admission to the hospital. No stones were found, but a hard pancreas was revealed. Instead of removal of the gallbladder a cholecystogastrostomy was performed, and, in addition, an appendectomy. The operation relieved him immediately from the daily pain which he had suffered.

This is one type of patient who will certainly have a recurrence of symptoms after cholecystectomy. Frequently such patients are subsequently classified as persons with neurasthenia. Some of them doubtless swell the ranks of those who continue to suffer after a noncalculous gallbladder has been removed for suspected gallbladder disease. Cholecystectomy in such cases may rob the patient of his best chance for symptomatic relief.

1738 Pine Street.

#### ABSTRACT OF DISCUSSION

DR. MAX THOREK, Chicago: There are still many weighty problems to be solved in the pathology and therapy of gallbladder disease. Much has been done in illuminating some paths which have been obscure, but there still are many problems which will be solved by constant cooperation among the clinician, the physiologist and the surgeon. From the etiologic point of view much attention should be paid to regurgitation of pancreatic juice into the gallbladder. The study of this subject has opened new avenues of approach which promise to yield good results. Dr. Behrend's observations on stones in the common duct are timely. The pendulum of opinion as to whether the common duct should be explored routinely is swinging back and forth. Hazards in operative procedure have been lowered by properly administered spinal anesthesia and should be resorted to more frequently but only under ideal conditions. The treatment of impacted stones in the common duct, particularly in the retroduodenal and ampullar portions, still remains a difficult surgical entity. The surgical division of strictures of the common duct low down is still an experimental procedure. The best way to treat injuries to the common duct is not to permit the common duct to be injured. I wish to recall Flint's aphorism on the great frequency of abnormalities in the distribution of the extrahepatic biliary passages and blood vessels. If one will keep this frequency constantly in mind and couple it with the fact that Hartmann's pouch often obscures, by enlargement and descent, the cystic duct, and if one will meticulously uncover the duct by pulling the pouch upward before proceeding to ligate it many injuries to the common duct will thus be avoided.

DR. JULIUS FRIEDENWALD, Baltimore: It is well recognized that the management of cholecystic disease is by no means always satisfactory, largely because the exact etiology of this disease is frequently difficult to establish. Although infection, biliary stasis and metabolic disease play an important role in the production of this disease yet the relationship of these various factors and their relative importance is far from clear and requires further study. On this account any additional evidence which may aid in clearing up this problem must be of value in leading to a more successful management of cholecystic disease. The Graham method of visualization of the gallbladder is of the greatest value in the diagnosis of cholecystic disease, but its limitations must constantly be borne in mind. While it presents evidence as to the contractility, concentrating power and deformity of the gallbladder as well as to the patency of the cystic duct, most important as these are, they are ordinarily indications of advanced pathologic conditions which often require surgical intervention. It does not, however, offer any information as to early cholecystitis—that

is, as to mucosal changes occurring at an early stage, evidence of which is usually obtained by means of biliary drainages, and thus at a period when medical measures are most effective; on the other hand, it may happen that the cholecystogram may be definitely positive for gallbladder disease, as is indicated by nonfilling, and yet normal conditions be revealed at operation. A number of such instances have occurred in my experience. It has been suggested in some of these cases that nonfilling may be due to disturbances outside the gallbladder, as, for instance, pyloric obstruction, duodenal ulcer or inflammatory involvement of the small bowel associated with diarrhea. It is important in formulating the therapeutic measures to be followed in cholecystic disease that one should not rely on the cholecystographic findings alone, although these are most valuable, but that these must be evaluated in relation to the history, physical findings, laboratory studies and biliary drainages. It is only in this way that the most satisfactory results can be expected.

DR. S. ALLEN WILKINSON JR., Boston: The author calls attention to a number of diseases of the common bile duct and to the relationship of chronic pancreatitis to this disease. I wish to mention a diagnostic procedure not discussed by Dr. Behrend which I have found of great advantage in the differential diagnosis of disease of the common duct, namely duodenal drainage. This is particularly true where a cholecystectomy has previously been done for gallstones and where the clinical history following the cholecystectomy may point either to cholangitis, coincident chronic pancreatitis or to stones of the common duct. These stones of the common duct may be either recurrent stones or ones left in at the time of the original operation. The history given by the patient is probably the most important single factor in this differentiation, but no other laboratory test except duodenal drainage offers any positive means of differentiation. When one examines the bile obtained from a drain, the presence of calcium bilirubin pigment and of cholesterol crystals almost invariably indicates the presence of stones. The author recommends a cholecystogastrostomy in cases of pancreatitis where the gallbladder is intact. I have seen a number of cases in which cholecystogastrostomy has been performed, followed by severe and disabling cholangitis produced by regurgitation of food into the gallbladder and thence into the biliary tract. For this reason I have given up cholecystogastrostomy and prefer to anastomose the gallbladder to the jejunum. By pulling up a loop of the jejunum the anastomosis is easy. It is made to a structure approximately similar in size and contour, and there is no tendency of the anastomosis to pull apart if the jejunum is anchored to the capsule of the liver. Physiologically, the effect is much better to introduce the bile into the jejunum rather than into the stomach, and the distressing postoperative nausea which some patients on whom anastomosis has been done is avoided. I am in agreement with Dr. Behrend when he condemns the practice of removing gallbladders which appear normal at operation and can go one step further and condemn equally heartily the practice of removing gallbladders which preoperatively may show a faint filling with the gallbladder dye or an incomplete emptying. There is no type of surgical procedure in which the end results after operation are poorer than they are after the removal of the noncalculous gallbladder for so-called chronic cholecystitis.

DR. HENRY A. RAFSKY, New York: Any classification which is of help should be utilized, but the problem in disease of the biliary tract is that many cases are encountered which are by no means typical. The patients most often relieved by cholecystectomy are those with calculous cholecystitis associated with attacks of biliary colic and to a lesser extent patients with noncalculous cholecystitis with severe abdominal pain. The use of microscopic examination of bile as a diagnostic and therapeutic guide should be emphasized. If we find a shower of cholesterol crystals combined with calcium bilirubin pigment in the duodenal contents we can be fairly certain that we are dealing with active disease of the biliary tract. I wish to carry this point one step further and stress the clinical importance of looking for crystalline elements in

the gastric contents, which can be performed routinely and is a comparatively simple procedure. Regarding a fall of the cholesterol esters below 70 per cent or a rise of the free cholesterol above 30 per cent as indicative of liver damage, I have found that the determination of the cholesterol partition serves as a good prognostic guide. Since using this test as a routine procedure before gallbladder operations for the past two years and guiding myself accordingly, I have not encountered a so-called liver death. This, I think, is more than a coincidental observation.

DR. A. F. ANDRESEN, Brooklyn: There are several points that should be emphasized, points that might be lost in the general discussions. There has been for a long time a feeling on the part of roentgenologists and surgeons that a lack of filling of the gallbladder indicates surgical intervention, and I think it was brought out nicely this morning that it should not be so considered. Many useless operations have been performed because of this misconception. In addition to the causes for nonfilling of the gallbladder with the dye which have been enumerated this morning and with which I agree, the most common reason is an insufficient stimulation to evacuation of the biliary tract occasioned by an inadequate diet. A patient with gastrointestinal symptoms may take insufficient amounts of food (especially fats) at insufficiently frequent intervals for considerable periods of time, and the resulting biliary stasis may cause so much concentration of bile in the gallbladder that the dye cannot permeate it or even enter the gallbladder. Promoting biliary drainage by a few weeks of frequent feedings containing adequate amounts of fat will often result in a beautiful filling of the gallbladder and may then demonstrate a normal gallbladder or one containing calculi. I am also glad that the speakers emphasized the need of fat in the diet. I have been trying for more than twenty years to convince people that fat has a necessary part in a gallbladder diet, and I am glad to see that gradually my idea is being adopted. One other point impressed itself on me in looking at one of the tables on the screen, and that was the emphasis on the old fallacy that painless jaundice indicates pancreatic carcinoma or, conversely, that pancreatic carcinoma is associated with painless jaundice. In an analysis of 40 patients made in our clinic recently, 60 per cent of them had pain and many severe pain in the midepigastrium or on one side or the other. We must not insist on painless jaundice to make a diagnosis of carcinoma at the head of the pancreas.

DR. MOSES BEHREND, Philadelphia: I must agree with Dr. Thorek concerning the injection of ether through the T tube to dissolve stones that have formed in the common duct, and the administration of amyl nitrite to relax the sphincter of Oddi. We, too, have not had much success with this treatment. All the patients on whom we tried it have had to be reoperated on. I can't agree with Dr. Thorek in regard to statistics. Twenty years ago I did a lot of anatomic research in this field and found 25 per cent of anomalies existed in the blood vessels and the ducts connected with the gallbladder tract. I agree with Dr. Wilkinson concerning duodenal drainage where the gallbladder has been removed. It is important to perform gallbladder drainage to determine whether new stones have formed in the common duct, even when the gallbladder has not been removed. The microscopic test of the presence of cholesterol crystals and pigment has given 100 per cent positive diagnoses. In this respect it has been a little bit better than the roentgen examination. I advocated many years ago that anastomosis of the gallbladder to the duodenum was much more preferable to anastomosis of the gallbladder to the stomach. I am sorry if I conveyed the feeling that I prefer cholecystogastrostomy to cholecystoduodenostomy. I do not believe that the danger is greater if the gallbladder is attached to the stomach than if it is attached to the duodenum or the jejunum. We have not performed a cholecystojejunostomy up to the present time. I am glad to hear the discussion concerning these two viscera and I hope in the future to use this method of anastomosis. The same dangers, however, may exist in hooking up the gallbladder to the jejunum as in the operation of cholecystogastrostomy and cholecystoduodenostomy.

SHOULD CORONARY DISEASE AND  
HYPERTENSION BE A CAUSE FOR  
REJECTION IN INDUSTRY?

H. M. F. BEHNEMAN, M.D.

SAN FRANCISCO

The answer to the highly controversial question "Should coronary disease and hypertension be a cause for rejection in industry?" depends to a great extent on who is asked—the injured worker, the employer, the trade union, the insurance carrier or the industrial physician. These are the people primarily involved in the solution of one of the most frequent yet most complicated problems confronting the student of industrial medicine. I use the word "student" because I know of no other pathologic problem in this specialty requiring more careful study in each individual case if the problem is at all concerned with industrial liability.

High in morbidity and highest in mortality, heart disease is the most expensive illness. More than a fifth of cardiac disorders occurs in persons under the age of 40, and it costs this country \$250,000,000 a year in lost wages, in addition to the cost of physical and financial dependence of persons with these disorders on the community and on industry. Furthermore, heart disease has a depressing and disintegrating effect within the family in which it occurs.

The compensation law of California specifically renders industry liable for "injuries arising out of or in the course of employment." High courts in other states have repeatedly decided that even a cardiac accident arising in the usual course of employment is compensable. Of the five interested parties mentioned previously the first four are inherently prejudiced from the start; therefore the physician qualified to review cases of cardiac disability in industry must be honest in order to be fair to all parties; he must be scientific to be thorough, in that he must have sound physiologic understanding of each case before he can come to a rational conclusion. The worker disabled by heart disease too often, but naturally, ascribes it to trauma or activity in his occupation. The employer is interested in efficiency, regular hours, speed and mass production. The trade union is concerned with the care and protection of its members. The insurance carrier wants to appease its assured yet show a profit for its stockholders without raising the employer's premium. Into this situation walks the physician employed by any of the previously mentioned parties to render an opinion or give expert testimony before a referee, judge or jury. The less said about the present status of so-called expert testimony, the better; what is needed is the creation of standards for qualification, to be defined and approved by physicians in each specialty in medicine.

The answer, then, to the question of industry's true course in the rejection of workers with heart disease and those in the hypertensive state can lie only in the merits of each such worker. Moreover, the answer rests on whether or not the applicant is applying for his first job with an employer or whether he has become disabled during the course of employment and reapplies for his job.

To any one with experience in the field of industrial medicine it is utterly absurd, and unfair to all con-

cerned, to attempt any blanket rejection of men willing to work just because they have cardiac or circulatory disorders. There's a job for the man and a man for the job, without detriment to either.

Consider the applicant for work who desires his first job with an employer. His case is simply and easily handled. If on thorough examination the man is found to have heart disease or circulatory hypertension, his acceptance or rejection should depend solely on whether the work he is to do will increase that disorder or whether the disorder will reduce his efficiency in that job. If either of these factors exists, rejection is warranted and is logical and best for all concerned. The disposition of such rejections will be mentioned later.

On the other hand, rejection or reemployment of the worker disabled on his job is a problem of great magnitude, the solution of which rests on many interrelated factors. To me the answer is plain. Rejection or acceptance should depend on the data obtained from a scientific and comprehensive study of each case. With this, then, as my premise, let me briefly but factually state the underlying mechanisms concerned in the production or exacerbation of heart disease and hypertension, on which, in turn, rejection hinges. But first a warning is in order. The physician in attendance must not assume the point of view of the private practitioner. In the latter's study of a patient there always lurks an automatic consideration of heredity, environment, family history, habits, character and other factors which determine one's longevity. In industrial medicine these things are not forgotten, but the law reads that the worker is entitled to compensation for "injuries arising out of and during the course of employment." The referee, judge and jury are little concerned in the physician's knowledge of the injured worker's family history, his background, stamina or stability, which are potent factors in health and disease. They want to know "Was or was not this man's illness, disability or death a result of the work he was doing?" Most workers are not physically examined before employment; if they are, a signed waiver on physical defects does not always legally protect the employer. Remember that even the exacerbation of a preexisting illness gives the worker (as well as dependents of the deceased) the same benefits and rights as if the work created the disease state. This is manifestly unfair, but it is the existing law, at least in unionized California, land of the three bridges.

Consider, then, what progression of events in an occupation could create coronary disorders and hypertension or exacerbate them to the point where industry would be called on to prove or disprove its responsibility. To do that physicians must proceed to fundamental physiologic facts enabling them to render a rational, scientific opinion. My own views are based on experience in such cases and on the conclusions reached from animal experimentation. I firmly believe that industry has not been held liable for cardiac disorders and hypertension in a vast number of instances in which it has been partially or wholly at fault. The majority of medical opinion rendered in California is against industrial liability.

Next, I feel industry should not be held liable for coronary and vascular accidents occurring when a worker is performing the usual routine activities of his job, with no unusual effort or exertion or trauma. In that case, one rightfully feels the disorder was approaching and the inevitable symptoms and signs were soon to appear regardless of the worker's activities. However, when a worker's heart disease arises from his

being subjected to trauma or activity bringing extraordinary or unusual effort in the course of his work it is difficult to see how his claim for compensation can be dismissed and his disease classed as of nonindustrial origin without a comprehensive examination; and these are my reasons for such an opinion:

The coronary system is practically the only supply of blood to the heart muscle. The heart's ability to increase its work depends on the oxygen supply. The minute anoxemia enters the picture the heart begins to fail. Heart failure is more pronounced in the hypertensive state, valvular disease and aortic abnormalities. The coronary blood flow depends on three factors: (1) aortic pressure, (2) mechanical resistance in the myocardium and (3) the caliber of the coronary vessels.

Arterial hypertension causes heart strain; it places a burden on the left ventricle, which develops the head of pressure for coronary flow. This ventricle can carry tremendous loads for years, but when it is partially anoxic its failure begins. When this occurs, however, in the right side of the heart there is far less ability of the right ventricle to carry on, with much faster failure when the pulmonary arterial pressure is increased. The speed and degree of failure, therefore, will depend on the unusual effort the heart is subjected to. Heart failure due to unusual effort is the more common type of acute or chronic myocardial failure. It is often produced in occupations which suddenly demand more exertion than the heart muscle can supply.

Now appears the question of industrial liability for death from coronary thrombi. Too often have I heard testimony to the effect that "Well, occlusion of this man's coronary vessels would have occurred soon, regardless of his work." It is true that the majority of published opinions have reported most coronary failures occur while the patient is at rest or asleep. But do not forget that hours to days usually elapse between the inception of a thrombus and its movement to occlusion. What right have physicians to say that inception took place at rest rather than at work, or that after inception the ensuing work did not speed up or increase the severity of the occlusion? After all, if a man labors five days at eight hours a day he is working forty out of a hundred and sixty-eight hours, which is less than a fourth of his week. Therefore his chances are three to one of having his attack when he's not working; but this fact provides no logical basis for excusing industry, for the hour of inception of a thrombus is all important.

Physical exertion and emotional states promote formation of thrombi, with resulting disaster. Again let me stress that if exertion has been the kind to which a worker has been usually exposed one should ascribe death to natural causes, but any degree beyond the usual, or exposure to toxic substances, temperature changes or oxygen deficiency warrants investigation of all circumstances when a cardiac accident occurs. Such an investigation must cover the period of time from the attack to a time at least a week previous to it.

Likewise, both physical exertion and highly emotional states produce hypertension of varying duration. Thus high intracapillary pressure is produced. In the presence of marked sclerosis or other forms of circulatory degeneration the capillary vessels are prone to give way, with resulting hemorrhage which, if large enough, becomes a damaging infarct. Various observers have found severe physical exertion raises blood pressure from 100 to 180 mm. of mercury. If the rupturing

capillary in itself does not produce interference in function, it initiates a train of events leading to future trouble.

Trauma of various kinds may also produce coronary closure, infarction and angina pectoris. I regret space does not permit the review of interesting and conclusive evidence. Penetrating and nonpenetrating blows to the chest and back have produced clearcut coronary disorders, the mechanism of production being due to vessel spasm. This may be transient, with little or no after-effects, or it may produce ischemia long enough to cause serious trouble. In workers buried in falling earth, increased intravascular pressure develops. Congenital defects may allow ordinary exertion but not unusual.

In other words, anything increasing the load of an inadequate heart muscle tends to produce heart failure, whether it be through coronary occlusion, spasm, rupture or aneurysm. Death may result from acute dilatation, as in electric shock, exposure to cold water and freezing temperatures. In the last war physicians saw the "nervous heart" with pain due to fatigue from persistent rapid beat. A worker with severe anemia cannot always respond to excess exertion without cardiac symptoms; in wounded patients the heart is affected by histamine shock; in those with burns, where blood is concentrated, there is diminished volume; in patients suffering hemorrhage there is an increased rate; in those with heatstroke death appears to occur from hemorrhage under the endocardium of the left ventricle. A heightened metabolism belabors the heart; diabetes accelerates sclerosis, and obesity accelerates coronary disease. A gain of 30 pounds (13.6 Kg.) in weight adds nearly 20 miles of blood vessels to our vascular system.

If the cardiac output is increased a rising blood pressure increases coronary flow, thus subjecting the diseased vessel to rupture if the dilating response to epinephrine is insufficient. Also, increased cardiac output (per beat) tends to tear debris from diseased valves as blood passes through, surging into the coronary openings of the aorta or into the general circulation. On the other hand, exertion may increase the circulatory rate without increasing the heart's output; then coronary pressure tends to fall and patients are in trouble, not from hemorrhage, but from anoxemia or clotting. Reversely, anoxemia in excess is a potent coronary vessel dilator. Why can't such dilatation in an atheromatous vessel be dangerous? Also an abrupt increase in the work of the heart or sudden lowering of pressure in the aorta starts a vicious circle which may result in coronary insufficiency. The resulting anoxemia causes a rapid circulatory rate resulting in an increase in the size of the right ventricle to a point where the all or none law does not apply—an increase leading to edema of the lungs; it is known that the right ventricle hasn't the reserve strength of the left one.

Moreover, body tissues and chemistry play a major role. On tissue metabolism depend the rate and volume output of the heart, which is merely an agent. The oxygen and carbon dioxide pressure, together with the hydrogen ion concentration in the capillaries, is the determining factor. During muscular work the circulation rate is considerably increased, both from the chemical side and from the fact that excessive breathing brings about a failure in circulation. Work increases oxygen consumption; when there isn't enough oxygen, through inability of the heart to produce it, the ensuing asphyxia impairs the action of the heart. Excess respiratory activity can cause shock, as forced breathing diminishes the circulation. This is particularly true in



the brain, which has a rich blood supply for its gray matter. Its normal oxygen pressure is very high; during muscular activity oxygen diminishes and carbon dioxide increases because of the venous blood from the muscles. The role of excess lactic acid formation is questionable. It is known, however, that when tissues are poorly supplied with blood unoxidized lactic acid accumulates in them and passes thence into the blood stream, raising the hydrogen ion and carbon dioxide concentration of the blood and followed by stimulation of the respiratory center.

Thus it can be seen that any factor producing even mild failure of the heart embraces multiple and complex changes in the whole circulatory system.

#### SUMMARY AND CONCLUSIONS

Augmented work increases oxygen consumption. When the entire heart is confronted with a general lack of oxygen the result is the picture of congestive failure; when there is a local lack of oxygen in the myocardium the result is angina pectoris, if mild, and infarction, if severe. The normal heart is usually able to meet the load placed on it by industry; there are few exceptions. Persons with abnormal hearts, circulatory hypertension and vascular diseases sometimes fulfil the demands made on them for a lifetime of activity but more often tend to fail eventually from even the routine activities and frequently fail when extraordinary activity is demanded. The presence of systemic disease is detrimental to normal circulatory function. Cardiac failure is in direct ratio to oxygen want. Exertion, disease and emotional states cause hypertension, which is usually a forerunner of coronary disease. The mechanism of production of coronary disease and hypertension has been reviewed in the light of their relation to industry.

Industry should reject workers with coronary disease and hypertension only when the work contemplated is clearly destined to exceed their ability to respond normally. Industry should accept responsibility for the pathologic conditions it has created or exacerbated. Industry and unions should cooperate by allotting work within the ability of the worker with heart disease, because 70 per cent of those rejected are able to work at something. Differentiation between ordinary and extraordinary activity is difficult but possible.

In conclusion I offer the following thoughts toward solution of this controversial subject:

1. Institute preemployment examinations with the right of the worker to sign a waiver which the law will recognize, thus acquainting the worker with his disabilities while protecting the employer.

2. In cases of questionable liability for cardiac disorders arising out of employment, demand careful medical analysis of each case by a competent examiner, who will painstakingly start his investigation not just from the time of onset of apparent disability but from a period many days previous thereto.

3. Establish wider use of electrocardiography, the value of which often exceeds that of the widely used roentgenography.

4. Amend the present industrial laws to allow finer gradations and degrees of incapacity.

5. Abolish the unfair laws extant in many states where a worker's death gives dependents full award when death has been due only to exacerbation of admitted, preexisting disease. Industry should rightfully reject a claim for full death benefits in the rupturing of an old syphilitic aneurysm at work which would have ruptured soon without any exertion; at present

there is little or no allocation of degree of responsibility. In California now the award is \$6,000 net.

6. Give the disabled worker prompt and proper medical care; rehabilitate him. Don't discard him, but develop him, and work with placement and rehabilitation bureaus which find work for disabled persons in skilled and unskilled labor.

7. Define more clearly in each state which occupational diseases are compensable and to what degree. As proposed by Robert T. Legge, create legislation enabling the person with heart disease to work under medical supervision yet releasing the employer and insurance carrier from financial liability in case of death.

8. At present, expert medical testimony is in a deplorable state. Create and define standards of qualification and urge their acceptance by commissions and courts.

9. Teach more industrial medicine in the nation's medical schools.

10. Create state medical boards of review which should decide which cases are worthy of consideration by commissions and courts. Such boards would eliminate many evils of the present system of decisions by lay referees, whose honest intentions are often buried in a mass of conflicting medical testimony.

Lastly, the principals must get together; the worker, the union, the employer, the insurer and the physician all have something to learn from one another.

That is my answer to the question before me. It cannot be a sweeping, conclusive one because it depends on the merits of the worker in each individual case.

This answer is a challenge to the industrial physician, especially when, with the vast defense program of the United States imminent, there will soon be a chance to place every available person. It is one I know will be met successfully to provide another brilliant chapter in the annals of American medicine.

450 Sutter Street.

#### ABSTRACT OF DISCUSSION

DR. NELSON D. MORRIS, Toledo, Ohio: I agree with Dr. Behneman that present knowledge does not warrant widespread rejection of workers for hypertensive or coronary disease. Adoption of such practice to protect the employer would implicitly force him to accept undue liability for those not rejected. Errors in courts or in legislative chambers in assigning undue risks to industry in re health of employees should not be allowed to stampee us into a false position. We have two important responsibilities: first, to safeguard and maintain health; second, to assist in determining causes in which injury attends occupation. Our first duty is performed by careful history taking, physical and laboratory examinations, reasonable effort to suit the task to the worker's capacity and continued supervision to find where we may be wrong, where physical status may change or where the conditions of labor may be improved. Industrial medicine so practiced aims to benefit every one through benefits conferred directly on the worker. It has no purpose to protect the employer from health risk except by keeping workers with known physical impairment from tasks of extra hazard and reducing those hazards wherever possible. The discharge of our second responsibility should not be confused by efforts to favor the interests of either worker or employer. Our obligation of impartiality is no less than that of the courts. If we give evidence or assume tasks unwarranted by our knowledge, we prejudice the decisions of judicial and legislative bodies. Unfair laws and unjust decisions reflect directly on members of our profession. Our duty is to know all that is knowable and to tell only what we know. We do not know the role of effort in creating or aggravating the condition in the vascular diseases under consideration. We can picture several possibilities for the victim

of thrombosis beginning during sleep. He may die without waking, feel pain and call help or get up in the morning unaware of what has happened. His first symptom may then occur while dressing, on his way to work, while doing his usual task or soon or late during unusual exertion. Then who is to say what was the role of effort in disabling or killing this man? If a worker suffers death with infarction without thrombosis under conditions of labor that might be termed accidental, and if his collateral vessels are found normal, his death may be attributed to industrial accident. But preliminary examination would hardly have saved the employer from such risk. For the present, we can be more efficient in the prevention of accidents than in the selection of workers able to withstand them.

DR. ROBERT T. LEGGE, Berkeley, Calif.: The question as to who can work is today an important problem. The employer in many instances would prefer to employ rejected men who have heart disease but are prohibited by compensation laws, increased insurance rates and the fact that a waiver is illegal. The unions are opposed to the changing of laws for any special legislation, fearing that it may invalidate the workmen's compensation act. The attitude of industrial physicians is in accord with the health programs for workers for preemployment and periodic examinations. The purpose is, of course, to improve efficiency of the individuals and to detect early defects that may arise in the course of employment. The vocational guidance committees of the various heart associations are definitely in accord in their efforts to solve problems by some uniform methods of class legislation, by special waivers or by the subsequent injury act. Dr. Behneman states that in California compensation is given in heart cases. Germany has a permanent disability provision requiring employers to carry 2 per cent of their injured. Such a measure should be adopted in our compensation laws. The National Institute for Cardiacs (Australia) not only secures employment for patients with heart disease but also guides and supervises them and establishes basic wages. America would be wise to adopt a like measure. Our knowledge today of coronary disease and hypertension warrants some modification of compensation laws in employing persons handicapped by heart disease, as the evidence here offered tends to substantiate. The Chicago Heart Association found that 1.34 per cent in thirteen industries were rejected on account of heart disease; 32.5 per cent of these were found able to go back to active service, while 42.2 per cent were restricted for modified duty. Master, Dack and Jaffe find only 2 per cent of coronary disease the result of effort. Berghoff, of Chicago, states that the mortality of coronary block is less than 10 per cent. Wychgel, in studies of arterial tension in steel workers 54 years of age, found that examinees with a systolic pressure of 200 and a diastolic pressure of 120 should be rejected.

DR. C. W. ROBERTS, Atlanta, Ga.: As a member of the Council on Industrial Health, I may be permitted to commend the section officers and the authors on the excellence of the program. This section of the Scientific Assembly is destined to grow as the rapidly expanding problems of industrial medicine are thrust on us. In an effort to extend the benefits of industrial medicine to the small plants in which most workers are employed, the Council on Industrial Health is vitally interested in the establishment of committees on industrial health in the various state associations, through whom it is believed that local postgraduate instruction may be provided. Your support of this movement is solicited.

DR. E. J. STIEGLITZ, Washington, D. C.: In connection with Dr. Behneman's paper I take some exception to the implied simplicity of the physiology of cardiac dynamics. I think that on further thought he would emphasize other factors, such as the availability of hemoglobin, the oxygen tension of the atmosphere, the availability of carbohydrate and insulin, which are all required by the myocardium. Furthermore, arterial constriction does not increase the pressure in the capillaries; it diminishes the blood supply distal to the narrowed arterioles. There is a definite slowing and sluggishness of the circulation distal to arteriolar constriction in hypertensive disease. A coronary accident, a coronary occlusion with or without infarction (and I have noticed the absence of any implication

of a quantitative sense in evaluating coronary thrombosis and its consequences on myocardial function), is but a phase of the disease arteriosclerosis. The patient is not well prior to his coronary accident and doesn't necessarily become permanently disabled thereafter. The coronary occlusion is merely an acute exacerbation of a process which continues to exist and will continue to exist until death. It may or may not progress rapidly, depending on many factors. We must not separate too sharply a phase of the disorder from the disease itself. A similar thought applies in hypertensive arterial disease. We must recognize that it is a progressive matter. Neither hypertensive disease nor arteriosclerosis is curable. Therefore we should not talk about "cure" to the patient, the employer or the insurance company. These disorders frequently are, however, controllable. In our statements to these persons, be they patients or prospective employees, we should emphasize "control" of their disorder rather than "cure." It is not a question of being well or sick, as though there were a sharp line of distinction between the two. I doubt that any one of us in this room is 100 per cent well. The major problem in these cases is not the height of the arterial tension at the time the man is up for employment or reevaluation of his health but the rate at which his disorder is progressing. Determination of the rate involves somewhat more of a clinical examination than is carried out in many industrial health surveys.

DR. ARTHUR M. MASTER, New York: I agree almost entirely with the suggestions made, but I should like to take issue with a statement that effort precipitates coronary occlusion. My associates and I have reported that from one half to one million attacks of coronary occlusion occur annually in this country. Hence it is important to determine whether effort can precipitate coronary occlusion or thrombosis. It will readily be admitted that effort can induce angina pectoris and failure of the left side of the heart with pulmonary edema and probably failure of the right side of the heart. However, there is no evidence that effort can precipitate a coronary occlusion. All persons exert themselves strenuously frequently during the day. Driving and parking a car, raising windows which do not give readily, are commonplace severe efforts performed repeatedly by most people. If effort were a factor in precipitating coronary occlusion, every one with coronary artery disease would have an occlusion. Furthermore, the latter occurs in all classes irrespective of occupation, again evidence that physical exertion is no factor in the formation of coronary occlusion. Recently it has been theorized that exertion increases the aortic pressure and thus ruptures a capillary in a coronary artery; this in turn is supposed to initiate a thrombus. There is no evidence for this. As Dr. Stieglitz says, a rise in arterial pressure is not transmitted to the peripheral capillaries. The area of the latter is so great that pressure falls precipitately. Again, Winternitz has shown that capillary rupture is part of the arteriosclerotic process, but nowhere does he intimate that effort or increase in blood pressure will rupture a capillary. In fact, Winternitz injected the coronary arteries of patients dying of coronary disease using the unheard of pressure of 500 to 1,000 mm. of mercury and yet did not produce capillary rupture!

DR. H. M. F. BEHNEMAN, San Francisco: I realized what a controversial question this was, but that is what makes it worthy of presentation at these meetings. Opinions of many of us in industrial work are molded not from what we were taught was the normal, ordinary course of events but from what we have learned by contact and experience over a period of time. I know of no industrial disease confronting the industrial physician more open to controversy than the relation of coronary disease to physical activity. California is highly unionized, particularly in San Francisco. Therefore the industrial physician in that community sees strong union pressure brought to bear in many of these cases. It has been my experience that the plaintiff in these cases is awarded a decision in his favor by the commission more often than it is denied him. This is true even though the majority of medical testimony may have been that the coronary attack was not caused or exacerbated by his labors. Such decisions to the contrary of medical opinion expressed at the hearing have been the inspiration of my plea to have a medical board of review. I could today cite many cases of men in advanced age spend-

ing years in sedentary occupations who are suddenly called on for excessive physical exertion and from that moment on have coronary disease of varying severity. Half of us here may say this sudden exertion played no part, and the other half might feel it did. Regardless of the physiology, such a case to a lay referee or jury is most often considered an industrial liability. A medical board of review could weed out many of these cases before they reach the commission.

## THE THERAPEUTIC SIGNIFICANCE OF PLASMA PROTEIN REPLACEMENT IN SEVERE BURNS

ROBERT ELMAN, M.D.

ST. LOUIS

Of the 5,000 deaths each year in the United States attributed to the effect of severe burns, many could undoubtedly be avoided by adequate replacement therapy in this serious type of injury.

An excellent clinical lecture on the treatment of burns is the recent one by McClure;<sup>1</sup> he has discussed the various theories of the etiology of death, among which are hepatic insufficiency, infection, toxemia, adrenal insufficiency and, finally, the theory which explains most of the general manifestations on the idea that there is an extensive loss of protein. It is this last aspect of the problem which I believe is the most important and which I wish to emphasize. This is of particular practical importance since it concerns the type and amount of fluids that are administered to a severely burned patient. It will be part of my purpose to present observations indicating that the type of fluid given is of decisive importance; the administration of dextrose and saline solution alone in burns is not only often ineffective but may, if excessive, be actually dangerous.

In saving the lives of severely burned patients a second point is worth emphasizing. There is among physicians a definite pessimism when confronted with an extensive burn, based on the inference that, since large areas of skin are involved, it will be impossible to obtain a sufficient amount of normal skin for skin grafting later. This idea is often erroneous as far as the burn turns out to be first or second degree and therefore requires no skin grafting whatever. It is obvious then that, if these patients could be carried over the acute stage of their disease and the general manifestations corrected, not only would lives be saved but further treatment would become unnecessary.

The historical background for the theory of protein loss in burns can be sketched briefly. It is interesting to note that almost a hundred years ago (1855) Buhl<sup>2</sup> observed a number of burned patients and noted changes similar to those produced in cholera, that is that there was in both a concentration of the blood with an increase in the concentration of the red blood cells and an extreme dryness of the skin and mucous membranes. In 1881 Tappeiner<sup>3</sup> studied four fatally burned patients as well as experimentally burned rabbits. Handicapped as he was by older analytic methods, his observations and conclusions agree essentially with more recently held ideas. Thus he clearly dif-

ferentiated the dehydration in cholera, which he said was due to loss of water, from that in burns, which he said was due to loss of plasma; he wrote "The concentration of the blood in burns occurs not through simple water loss but by loss of a fluid whose composition of solids is close to that of blood plasma." His therapeutic implications sound startlingly modern, i. e. "I consider as the cause of death in severe burns the concentration of the blood produced by transudation of plasma-rich fluid in the burned skin and recommend therapeutic transfusion of serous fluid." Although a good many observations were made in the succeeding decades, and especially during the last great war, an intensive study of burns was made by Underhill<sup>4</sup> and his co-workers after a theater fire in New Haven, Conn., in 1923 during which twenty-one victims were studied at the New Haven Hospital. Underhill<sup>4</sup> in 1927 expressed his views as to the treatment of burns as follows: "In treatment of burns, therefore, the essential object is to keep the blood concentration near a normal level until the blood capillaries in the skin injured by the heat have had an opportunity to repair themselves and again become capable of holding within themselves the fluid of the blood in a normal manner." This, he estimated, requires from twenty-four to forty-eight hours. Although he recognized the fact that the

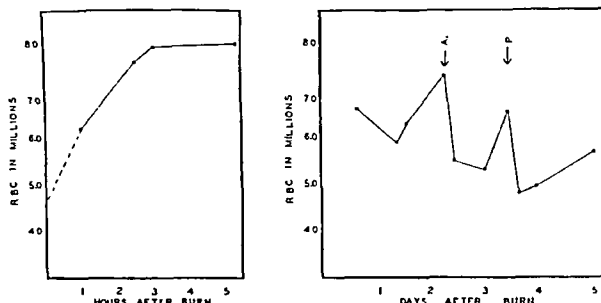


Figure 1 (case 1):

Figure 2 (case 2):

Figs. 1 and 2.—These graphs represent the red blood cell counts of two burned patients in the St. Louis City Hospital. The first patient, a woman aged 25, was admitted at 6 p. m. on July 5, 1935, and died six hours later. The second patient, a woman aged 30, was admitted April 10, 1935, and died six days later. In both cases large amounts of parenteral dextrose and saline solution were injected. In figure 1 note the failure to influence the concentration of the blood, although 6,000 cc. of dextrose and saline solution was injected in four hours. In figure 2 the prompt effect of 400 cc. of acacia (A) as well as 450 cc. of plasma (P) in lowering the red blood cell count is clearly seen. Other fluids to the extent of from 6,000 to 8,000 cc. a day were relatively ineffective.

blood concentration was due to loss of plasma rather than of water and electrolyte, he recommended only the injection (or the ingestion) of a large amount of simple fluids. In a monograph published in 1930 by Pack and Davis,<sup>5</sup> the use of transfusions is mentioned but these authors stated that "Intravenous saline solution and glucose venoclysis are inexpensive and more than satisfactory substitutes for blood because they are dilutants of the concentrated blood and, moreover, flush the kidneys of toxin." A few years later, in 1933, McIver<sup>6</sup> reported considerable data in a series of extensive cutaneous burns and noted that the blister fluid was like plasma and contained 3.7 per cent of total protein. He stated, therefore, that "loss of fluid is not simply a loss of water content of blood but of a substance that is closely parallel to whole plasma." In

Read before the Society of Clinical Surgeons, St. Louis, April 29, 1940.  
From the Department of Surgery, Washington University School of Medicine, and the Barnes, St. Louis Children's and St. Louis City hospitals.

1. McClure, R. D.: The Treatment of the Patient with Severe Burns, J. A. M. A. 113: 1808 (Nov. 11) 1939.

2. Buhl: Epidemische Cholera, Ztschr. f. rat. Med. 6: 1, 77, 1855.

3. Tappeiner: Ueber Veränderungen des Blutes und der Muskeln nach ausgedehnten Hautverbrennungen, Centralbl. f. d. med. Wissensch. 21: 383, 401, 1881.

4. Underhill, F. P.: Changes in Blood Concentration with Special Reference to the Treatment of Extensive Superficial Burns, Ann. Surg. 86: 840 (Dec.) 1927.

5. Pack, G. T., and Davis, A. H.: Burns, Philadelphia, J. B. Lippincott Company, 1930, p. 115.

6. McIver, M. A.: Study in Extensive Cutaneous Burns, Ann. Surg. 97: 670 (May) 1933.

the treatment of his patients, however, plasma transfusions were not used, and he does not mention this form of therapy.

A large series of experimental studies on cutaneous burns have been made especially during the past decade; these will not be summarized here since they were reviewed by Harkins and Harmon<sup>7</sup> in 1937. Suffice it to say that all these studies have definitely demonstrated that, following a severe burn, there is a tremendous loss into the burned area of a fluid which has a composition which is close to that of plasma. Indeed, Blalock and his co-workers showed that the loss of plasma alone could itself be of sufficient magnitude to produce symptoms of shock.

Direct measurements of plasma protein of burned patients were reported by Davidson and Matthew<sup>8</sup> in 1927. They observed six cases and found relatively little change in the total plasma protein, although there was a fall in the albumin and a rise in the globulin fraction. Such observations, in view of the concentration of the red cells, really mean loss of plasma protein, because if water and electrolyte alone were lost as in other types of dehydration the serum protein would be more concentrated.<sup>9</sup> Davidson and Matthew<sup>8</sup> therefore did not advise the use of plasma transfusions or blood in the treatment of severe burns. It is of interest, however, to note that in 1921 Robertson<sup>10</sup> described

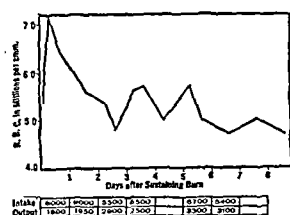


Figure 3 (case 3).

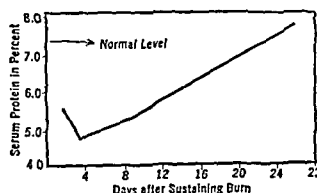


Figure 4 (case 4).

Figs. 3 and 4.—These graphs show the behavior of the red blood cells and serum protein in two cases of severe burn. Note in figure 3 the high red blood cell count, which was permanently relieved only after six days, in spite of a tremendous fluid intake. (The figures for intake and output are in cubic centimeters.) Note also the low urinary output during the first few days; obviously much of the injected fluid escaped into the tissues, both normal as well as burned areas. In figure 4 note the low serum protein, which required four weeks before restoration was complete in spite of a high caloric, high protein diet (copied from Cole and Elman<sup>11</sup>).

six severely burned children in whom dramatic therapeutic effects followed the use of large transfusions. However, four of these children were bled before the borrowed blood was injected. This now discredited procedure of exsanguination-transfusion is based on the idea that death is due to a toxin in the circulating blood. It is obvious, moreover, that exsanguination played no role, because Robertson obtained the same beneficial results on patients given a transfusion without a preliminary exsanguination. It is significant to note that this worker used large amounts of blood, e. g. he injected as much as 400 cc. into a 2 year old child.

My interest in burns was stimulated in 1935 following a serious sewer explosion in St. Louis during which many workmen were severely burned. In 1936 in a brief report by Weiner, Rowlette and Elman<sup>9</sup> data on forty patients with severe burns treated at the

St. Louis City Hospital were given; a very definite relative as well as actual fall in the concentration of the serum protein was observed. It was pointed out too that large amounts of dextrose or saline solution were deleterious in that edema might be provoked thereby. The use of large plasma transfusions and a large protein diet was described and advocated in this paper. In the "Textbook of General Surgery," appearing first in 1936, Cole and Elman<sup>11</sup> made the statement that "too much fluid may be deleterious unless urinary excretion is adequate because it is apt to produce a general edema. . . . True replacement therapy, therefore, should consist of intravenous injection of blood plasma." More recently Lucido,<sup>12</sup> also at the St. Louis City Hospital, observed that a severely burned patient excreted large amounts of nitrogen in the urine and that this evidence of excessive destruction of protein was an additional reason for the administration of a large protein intake in these severely burned patients.

Within the past year or two there has been a growing realization of the importance of plasma loss in burns and the application of this idea to the treatment of severely burned patients in that large amounts of plasma protein must be injected in order to achieve a beneficial therapeutic effect. The report of Trusler, Egbert and Williams<sup>13</sup> as well as that of Elkinton, Gilmour and Wolff<sup>14</sup> should be mentioned in this connection. The observations of these two series of workers agree essentially with ours as reported in 1936, which are described in more detail and extended by the evidence now to be presented.

#### PRESENT OBSERVATIONS

The ineffectiveness of dextrose and saline solution in correcting the red blood cell concentration is illustrated in several charts representing cases in which frequent red cell counts were done. This is a simple and usually accurate clinical method of following the changes in relative plasma volume. It will be seen in case 1 (fig. 1) that 6,000 cc. of parenteral fluid had no effect in halting the increasing dehydration which finally led to death six hours after admission. In contrast is the red blood cell curve in case 2 (fig. 2), in which the prompt effect of acacia on one occasion and plasma on another in lowering the red blood cell count is shown. In case 3 (fig. 3), although large amounts of dextrose and saline solution were administered, it required five days before there was a permanent fall in the red blood cell count. Urinary output was low during this period in spite of the large intake; obviously much of the injected fluid was accumulating in the tissues even though edema was not evident. In case 4 (fig. 4) the low serum protein is shown as well as its slow return to normal, requiring four weeks.

As an example of the dramatic effect of adequate transfusions, the following case is described, the details of which were kindly given me by Dr. N. A. Womack:

CASE 5.—W. M., a boy aged 3½ years (weight 15 Kg.), was admitted to the St. Louis Children's Hospital Sept. 12, 1938, one hour after his clothes had caught fire from a blow torch. It was estimated that 40 per cent of his body was involved; this was evident from the subsequent course. He

7. Harkins, H. N., and Harmon, P. H.: Plasma Exudation, *Ann. Surg.* 106: 1070 (Dec.) 1937.

8. Davidson, E. C., and Matthew, C. W.: Plasma Protein in Cutaneous Burns, *Arch. Surg.* 15: 265 (Aug.) 1927.

9. Weiner, D. O.; Rowlette, A. P., and Elman, Robert: Significance of Loss of Serum Protein in Therapy of Severe Burns, *Proc. Soc. Exper. Biol. & Med.* 34: 484 (May) 1936.

10. Robertson, B.: Blood Transfusion in Severe Burns in Infants and Young Children, *Canad. M. A. J.* 11: 744 (Oct.) 1921.

11. Cole, W. H., and Elman, Robert: *Textbook of General Surgery*, New York, D. Appleton-Century Company, 1936, p. 309.

12. Lucido, Joseph: Metabolic and Blood Chemical Changes in a Severe Burn, *Ann. Surg.* 111: 640 (April) 1940.

13. Trusler, H. M.; Egbert, H. L., and Williams, H. S.: Burn Shock, *J. A. M. A.* 113: 2207 (Dec. 16) 1939.

14. Elkinton, J. R.; Gilmour, M. T., and Wolff, W. A.: Control of Water and Electrolyte Balance in Surgical Patients, *Ann. Surg.* 110: 1050 (Dec.) 1939.

had already been given a sedative of morphine; he was debrided in a tub of warm water without further sedation. A continuous venoclysis was then started and 300 cc. (20 cc. per kilogram) of whole citrated blood given the same evening. Although he vomited, his general condition was good following the blood transfusion and the injection of intravenous fluids but by the next morning, twenty hours after the burn, he was semicomatose and had generalized convulsions. A second transfusion of 300 cc. plus 5 cc. of adrenal cortex extract was given at 8 a. m. Following this the patient was more alert but slumped again the second night, so that the next morning he was given a third transfusion of 300 cc., following which he was alert and rational and began to take fluids by mouth. The fourth day he received a fourth transfusion of the same amount and by the next day all fluids were taken by mouth and he made an uneventful recovery, being discharged October 14, thirty-two days after admission, with no loss of skin, the burn healing spontaneously without scar and without the necessity of skin grafting. He received during the first four days a total of 1,200 cc. of blood in addition to other parenteral fluids.

#### COMMENT

Loss of protein is clearly an important and serious effect of severe cutaneous burns. This loss affects not only tissue protein but plasma protein. Moreover, it seems likely that many if not all of the general manifestations of severe cutaneous burns are connected with this loss. As far as the plasma is concerned, it is obvious that fluid containing only dextrose or saline solution alone will not of itself replace this loss because of the essential need for plasma protein. This need is due to the importance of maintaining the osmotic pressure of the circulating blood. Fluid without colloid properties when injected intravenously soon escapes from the blood bed and fails to relieve the essential hemoconcentration (fig. 5). The effectiveness of acacia (fig. 2) points to the importance of colloids in keeping fluid within the blood vessels.

The magnitude of replacement therapy designed to meet the plasma loss is not generally realized. It is therefore important to point out that 20 cc. of blood per kilogram of body weight, repeated each day for four days, was necessary in the reported case. This would correspond in an adult to transfusions totaling 5,500 cc. of whole blood. Anything less would probably not replace the large amount of lost plasma protein. Although true replacement therapy would consist of plasma transfusion, it is probable that unless plasma can be obtained readily whole blood is just as effective even though the red cells are really not needed.

In general we have given plasma to children in single doses of 10 cc. per kilogram of body weight, repeated as frequently as necessary. Recently we injected with dramatic results 200 cc. of plasma three times in forty-eight hours in a girl weighing only 18 Kg. Because of the practical problem involved in giving 1,500 cc. of blood to an adult, the possibility of supplying at least part of the lost protein by the injection of amino acids is pertinent. While such a method of parenteral protein replacement is practical, its use in burns awaits clinical trial. I have not used amino acids because of the possible difficulty in promoting serum albumin synthesis in this way and because it seemed more direct to replace the lost protein by plasma transfusions, since the loss is acute and requires treatment for only a few days. Nevertheless, it may prove a great practical advantage to inject amino acids to supply much of the need for tissue protein, combining it with a relatively small transfusion to supply the need for the serum protein. Observations along this line are now being made.

As a substitute for plasma protein, acacia has been used because of its colloidal properties (case 2). The beneficial effects of acacia are definite and such a solution is far superior to dextrose and saline solution alone. Obviously, however, acacia is a foreign substance and if given in large amounts may be taken up by the liver and interfere with hepatic function. If possible, therefore, plasma is definitely preferable. I would use acacia only once and even then only in an emergency while waiting for the preparation of whole blood or plasma.

The value of adrenal cortex extract has been questionable in our experience. It was given in case 5 along with repeated and large transfusions. In other cases in which smaller or no transfusions have been given it has been used repeatedly without effect. On the other hand, it is important to note the recent clinical and experimental observations of Wilson and Stewart,<sup>15</sup> who have found significant benefits following the use of the synthetic adrenal cortex hormone desoxycorticosterone acetate.

The local treatment of the burned area, while not a part of the present discussion, probably does have some influence on the degree of plasma loss and especially on the tendency to infection, which, when it occurs, leads to increases in protein loss by way of the extensive purulent exudation. In the local treatment, therefore, adequate, thorough cleansing and débridement is essential even if general anesthesia has to be used to do so. Proper protection of the wound after this is carried out is important in order to prevent secondary infection and to assure the comfort of the patient largely by relieving pain. These ends, in my experience, are best subserved by an adequately made dry crust over the area. A simple method which we use at the St. Louis City Hospital is the application of silver nitrate 10 per cent and tannic acid 20 per cent alternately not only over the obviously burned area but well beyond, until a line of demarcation is visible. I have repeatedly observed that when infections occur they start at the edge of the burn and usually at an inadequately cleansed or improperly tanned zone.

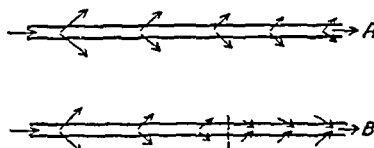


Fig. 5.—Diagram of the fluid flow in the capillaries, which act as a semipermeable membrane and illustrate the effects of Starling's hypothesis (Schade, H.; Claussen, F., and others: *Ztschr. f. d. ges. exper. Med.* 49: 334, 1926). A, fluid escapes from the lumen into the tissue spaces when osmotic pressure is low, owing to the absence of colloids in the blood. This occurs when dextrose and saline solution is injected into a burned patient who has lost a large part of his blood colloids (plasma protein). B, the normal condition; note that fluid flow from the lumen is limited whereas passage of fluid from the tissue spaces to the lumen occurs. This behavior is due to the presence within the capillary lumen of blood which has a high osmotic pressure owing to its high colloid (protein) content.

#### SUMMARY

The general manifestations of a severe burn develop rapidly; if they are combated promptly, many lives will be saved. These manifestations are due largely to rapid and extensive loss of both tissue and especially plasma protein. Replacement of the latter by plasma transfusion is essential to maintain the circulation and to relieve the concentration of the blood. The magnitude of the plasma loss is such that 10 cc. of plasma or 20 cc. of whole blood per kilogram of body weight

15. Wilson, W. C., and Stewart, C. P.: Changes in Blood Chemistry After Burning Injuries, *Tr. Med.-Chir. Soc. Edinburgh*, 1938-1939, p. 153; in *Edinburgh M. J.*, November 1939.

may have to be given and be repeated if necessary. A high protein diet is also necessary as soon as nourishment by mouth is possible. The intravenous injection of amino acids as a partial or complete substitute for plasma transfusion awaits clinical trial. A single injection of acacia may be used if no blood is available, but it is greatly inferior to plasma. The injection of large amounts of dextrose and saline solution alone in severe burns may prove not only ineffective but may even produce deleterious results. Since many severe burns may not require skin grafting, the therapeutic problem is largely one of combating the general manifestations.

Euclid Avenue and Kingshighway.

## MEDICATION IN THE CONTROL OF PAIN IN TERMINAL CANCER

WITH REFERENCE TO THE STUDY OF NEWER  
SYNTHETIC ANALGESICS

LYNDON E. LEE JR., M.D.

BOSTON

My purpose in this paper is to emphasize certain facts and modes of thought which it is hoped will cross the mind of the reader when next he encounters a patient suffering the pain so frequently attending the terminal phase of incurable cancer.

It is essential that the observer assure himself that this is a terminal case, that all avenues of therapy have been blocked, all methods of treatment exhausted, and that the comfort of the patient is the only thing for which he can hope. Even at this point it is incumbent on the physician to be on the alert for any sign which might indicate that new therapy or further treatment might promise a period, however short, of useful existence.

Most obvious and most essential among the measures to insure the patient's enjoyment of his last weeks of life is the question of adequate nursing care. While the patient is able to care for himself fairly well he may be managed at home, but when he has reached the stage where his is a bed and chair existence or where frequent attention is necessary he is best cared for in some institution. Here the correct execution of the doctor's orders is more certain and the family is spared the ordeal of watching each minute of the patient's decline. Frequent changes of linen, special precaution to prevent decubitus and the cleaning and dressing of draining or raw surfaces as well as provision for the minor surgical procedures which go so far in maintaining psychologic and physical ease are best attended to by nurses trained in this work. But here I would make the plea for temporary omission of the bustling routine of the daily bath or vigorous bed change if the patient is suffering a particularly bad day.

The use of some soothing or anesthetic topical application to painful ulcerated areas or regions subject to irritation, as in the vulva in cases of carcinoma of the cervix with vesicovaginal or rectovaginal fistula, may decrease the necessity for stronger analgesics. For this

purpose benzocaine ointment 7 per cent has been found very useful. It has been used for periods up to six months with frequent daily applications without apparent harm or loss of effectiveness.

Careful attention to an adequate diet, particularly in reference to fluid and vitamin intake, is essential in helping to maintain the patient in comfort. Special care to the function of the bowels and bladder may be considered another must.

Aside from the nursing aspect, measures for controlling pain in the cancer patient may be listed as roentgenologic, surgical and medicinal. Choice of a method in any specific case should be based on the known life expectancy and known reaction to therapy in the particular cancer type with which one is dealing.<sup>1</sup> Medication for analgesia is placed at the end of this list knowingly, for it is well to exercise the other procedures before, not after, the effectiveness of medication has been exhausted. The suitable patient going early to the roentgenologist or neurosurgeon for palliation is a far better risk and is given more complete and permanent relief of pain through these measures than through any known medication. Other procedures for pain control, notably freezing,<sup>2</sup> are still in the experimental stage and as such are best confined to the larger research centers under the supervision of specially trained and skilled investigators.

TABLE 1.—Daily Evaluation of Abstinence Syndrome Intensity by the Point System

Signs	Points
Yawning .....	1
Lacrimation .....	1
Rhinorrhea .....	1
Diaphoresis .....	1
Anorexia (40% drop).....	3
Mydriasis .....	3
Tremor .....	3
Gooseflesh .....	3
Restlessness .....	5
Emesis (each) .....	5
Temperature (daily average) each 0.1 C. increase over addition mean .....	1
Respiration (daily average) each respiration per minute over addition mean .....	1
Systolic blood pressure (a. m.) each 2 mm. Hg rise over addition mean (15 point limit).....	1
Weight (a. m.) each pound lost from last addition day.....	1
Total abstinence syndrome intensity daily is sum of points scored	

In consideration of medicinal analgesia, one may pass quickly over the coal tar analgesics, pausing only to mention that they be given a trial. Their inadequacies in controlling the borings, aching, stabblings and burnings of advanced cancer are well recognized, but an adequate trial is justified by their surprising efficiency in some cases. It is interesting to note that work by Hardy and Wolff at New York Hospital suggests that acetylsalicylic acid is of little use as an adjunct to the phenanthrenes, opiate synergism not being demonstrable

1. Nathanson, I. T., and Welch, C. E.: Life Expectancy and Incidence of Malignant Disease: Carcinoma of Breast, *Am. J. Cancer* 28: 40-53 (Sept.) 1936; Carcinoma of Gastro-Intestinal Tract, *ibid.* 31: 457-466 (Nov.) 1937; Malignant Lymphoma, Fibrosarcoma, Malignant Melanoma and Osteogenic Sarcoma, *ibid.* 31: 598-608 (Dec.) 1937. Daland, E. M.; Welch, C. E., and Nathanson, I. T.: One Hundred Untreated Carcinomas of the Rectum, *New England J. Med.* 214: 451-455 (March 5) 1936. Peller, S.: Life Expectancy and Mortality from Skin (March 5) 1936. *Am. J. M. Sc.* 109: 449-458 (April) 1940. Ewing, J.: and Lip Cancer, *Am. J. M. Sc.* 113: 653-660 (Aug. 19) 1937. Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928. Cutler, M., and Buschke, F.: Cancer, Its Diagnosis and Treatment, Philadelphia, W. B. Saunders Company, 1938.

2. Smith, L. W., and Fay, T.: Temperature Factors in Carcinoma and Embryonal Cell Growth, *J. A. M. A.* 113: 653-660 (Aug. 19) 1937. Gerster, J. C. H., and others: General Cryotherapy: Symposium, *Bull. New York Acad. Med.* 16: 312-340 (May) 1940.

Read before the Section on Radiology at the Ninety-First Annual Session of the American Medical Association, New York, June 12, 1940.

The work reported in this paper is part of a unified effort by a number of groups to solve the problem of drug addiction. The participating organizations have been the Rockefeller Foundation, the National Research Council, the United States Public Health Service, the United States Bureau of Narcotics, the University of Virginia, the University of Michigan and the Massachusetts Department of Health.



by the ingenious experimental method of Wolff, Hardy and Goodell.<sup>3</sup>

One of the newer analgesics, cobra venom, deserves further mention on the basis of reports which have been appearing in the literature.<sup>4</sup> The material was first used by the French but has been popularized in the United States by Macht. Reports on the various series studied clinically do not indicate that the work has been adequately controlled. Use of the material in 8 cases, a group acknowledged to be inadequate for statistical significance, has failed to justify the enthusiastic reports. Of the 8 patients only one seemed to experience any relief from pain, and this was not by any means complete. Further study is being carried on and a later report is anticipated. However, on the basis of experience recorded by others, the material may be given a trial before the patient is condemned to the use of narcotics.

As yet no analgesic as efficient as the morphine group has been developed. This includes codeine, morphine, heroin and dihydrid. All are based on the same chemical foundation (fig. 1). A definite cross tolerance among them exists, so that one cannot expect to exhaust the effectiveness of one, then turn to the use of another with the hope that it will function to the degree it might have had if the patient had no previous narcotic experience.

The use of narcotics in the terminal cancer is to be condemned if it can possibly be avoided. Morphine and terminal cancer are in no way synonymous. Morphine usage is an unpleasant experience to the majority of human subjects because of undesirable side effects.<sup>5</sup> Dominant in the list of these unfortunate effects is addiction.

There were, according to the best estimates, approximately one hundred thousand addicts in the United States in 1924 and Kolb,<sup>6</sup> who published these figures,

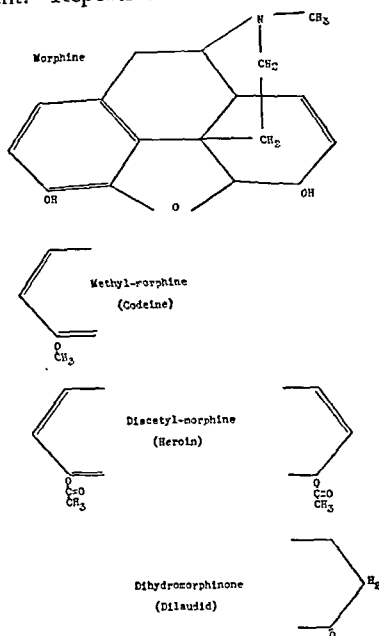


Fig. 1.—Structural formulas of morphine, codeine, heroin and dilaudid.

estimated that 14 per cent of these were normal persons accidentally addicted during therapy for pain. It is safe to say that this percentage is not lower today and it may increase as the number of inebriate addicts decreases through more effective control of their narcotic supply. This group of the unavoidably or inadvertently addicted is in particular the concern of the responsible physician. These people are suffering from what has become recognized as an actual disease. The disease is evidenced by increasing tolerance to and eventual dependence on the presence of an adequate amount of one of these drugs in the body. Such a state of dependence, addiction if you like, may develop in as short a time as three weeks of drug administration.<sup>7</sup> The presence of this state of dependence can be demonstrated only by the development of characteristic abstinence symptoms following withdrawal from the drugs. These phenomena may be listed as yawning, lacrimation, rhinorrhea, perspiration, goose flesh, mydriasis, tremor, restlessness, emesis, diarrhea, an increased temperature, increased respirations, increased blood pressure and decreased weight—all of which can be almost quantitatively observed<sup>8</sup> (table 1).

In addition, the patient frequently complains of cramps in the calves and abdomen, insomnia, weakness, anorexia, the presence of foul odors or tastes, lack of appetite and lack of desire to smoke. He may suffer priapism or pollutions. If a female, she may experience return of an inhibited menstrual flow. The development of this syndrome follows a typical pattern coming on, not abruptly on withdrawal, as is so often supposed, but gradually, reaching an unmistakably definite intensity on an average of fifteen hours following the last dose of narcotic. The syndrome increases in severity to the twenty-fourth hour, maintains this level of greatest severity for twenty-four to thirty-six hours and gradually falls to normal at about the seventh day<sup>9</sup> (fig. 2).

However, without withdrawal, dependence may be suspected in the patient who is receiving diminishing

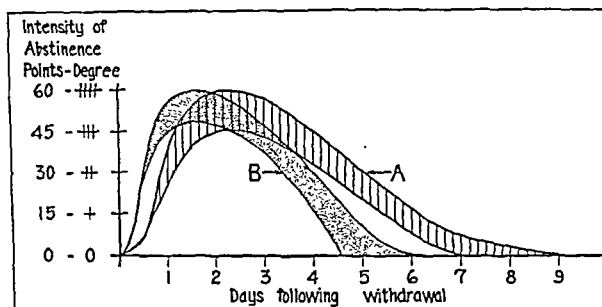


Fig. 2.—Two types of abstinence syndrome.

returns in analgesia with increasingly large doses of narcotics. This dependence, this addiction, is not to be condemned in the terminal cancer patient on moral or ethical grounds but on the very real factor that with dependence comes loss of analgesic effectiveness. If the patient may live more than three to four months, it is especially important that neurosurgery or palliative

3. Hardy, J. D.; Wolff, H. G., and Goodell, H.: Studies on Pain Sensation: I. Measurement of Pain Threshold with Thermal Radiation, *Am. J. Physiol.* **126**: 523 (July) 1939. Wolff, H. G.; Hardy, J. D., and Goodell, H.: II. The Quantitative Analysis of the Action of Analgesics, *ibid.* **126**: 656 (July) 1939.

4. Orticconi, A.: A propos de l'action du venin de cobra dans le traitement des algies et des tumeurs, *Presse méd.* **42**: 112-114 (Jan. 20) 1934. Macht, D. I.: Action du venin de cobra sur le sens de la douleur chez l'homme et chez le cobaye, *Compt. rend. Soc. de biol.* **120**: 286-289, 1935. Therapeutic Experiences with Cobra Venom, *Ann. Int. Med.* **11**: 1824-1833 (April) 1938. Taguet, C.: La cure des algies et des tumeurs malignes, *Bull. et mém. Soc. de méd. de Paris* **137**: 310-311 (April 29) 1933. Rutherford, R. N.: Use of Cobra Venom in Relief of Intractable Pain, *New England J. Med.* **221**: 408-414 (Sept. 14) 1939.

5. Kolb, L.: Pleasure and Deterioration from Narcotic Addiction, *Ment. Hyg.* **9**: 699-724 (Oct.) 1925; Reprint 211, National Committee for Mental Hygiene, 1925.

6. Kolb, L., and Du Mez, A. G.: Prevalence and Trend of Drug Addiction in the United States and Factors Influencing It, *Pub. Health Rep.* **39**: 1179-1204 (May) 1924; Reprint 924, United States Treasury Department, Public Health Service, 1924.

7. Seeleth, C. E.: A Rational Treatment of the Morphine Habit, *J. A. M. A.* **66**: 860-862 (March 18) 1916. Lambert, A.: The Doctor and the Drug Addict, Philadelphia County Medical Society Symposium November 10, 1920.

8. Kolb, L., and Small, L. F.: Clinical Studies of Drug Addiction, *Treatment of Drug Addiction*, Pub. Health **18**.

9. Kolb, L., and Himmelsbach, C. K.: Clinical Studies of Drug Addiction, *Am. J. Psychiat.* **94**: 759-799 (Jan.) 1938. Studies on Drug Addiction, Small, L. F.; Eddy, N. B.; Mossetig, E., and Himmelsbach, C. K.: *Pub. Health Rep.*, 1938, supp. 138, pp. 1-143.



it must be said that every effort has been made to keep the observations as objective as possible and free from any prejudice.

At the Pondville Hospital particular attention has been directed to the effectiveness of a new substance in comparison with morphine in terminal cancer and to the readiness with which tolerance and dependence are developed in such cases. To this end patients have been selected on the basis of (1) intelligence and cooperativeness, (2) lack of previous narcotic experience, (3) general physical condition, (4) terminal stage of their disease, (5) degree of pain as far as it could be determined, (6) necessity for continued hospitalization. Various preliminary tests had proved one drug more promising than all others developed in the cooperative study sponsored by the National Research Council. This drug was methyl dihydromorphinone.<sup>11</sup> Based on observation of the effects of eight thousand doses, the use of a 5 mg. dose of this substance in comparison with a 10 mg. dose of morphine is shown in table 2.

Tolerance to and dependence on methyl dihydromorphinone develop less rapidly than to morphine. Its hypnotic effect is less marked and of shorter duration. Fewer side effects have been observed in its use. After periods of temporary withdrawal, eight to fifteen hours, it has not been possible, on readministration of morphine, to obtain relief with less than the amount admin-

TABLE 2.—Results of Morphine 10 Mg. and Methyl Dihydromorphinone 5 Mg.

	Morphine	Methyl Dihydromorphinone
Duration of relief.....	3 hours 29 minutes	2 hours 48 minutes
Time dose to relief.....	26 minutes	23 minutes
Hours sleep per dose.....	1 hour 53 minutes	1 hour 38 minutes
Respiratory depression (at 30 minutes)	0.9 respiration per minute	1.2 respirations per minute

istered at the last dose before temporary withdrawal. It has been regularly possible, on readministration of methyl dihydromorphinone, to get relief with a smaller amount than was administered at the last dose before withdrawal. Frequently it has been possible to reduce the dose to the amount used in initiating narcotic administration. This factor alone is of tremendous importance in prolonging the period of continued analgesic effectiveness. The material has been used in cases for over six months without alteration in this factor.

It must be stated, however, that this material, methyl dihydromorphinone, remains to the present time a laboratory and clinical curiosity. The cost of its production is prohibitive, and it is not yet felt that sufficient clinical work has been done to warrant its return to the chemist for further study in regard to its production on a commercial basis. We are in hopes that an even better drug may eventually be provided.

#### CONCLUSIONS

Review of the facts and opinions here stated leads to the conclusions that:

1. Nursing, roentgenologic and surgical measures for controlling pain should be given precedence over chemotherapeutics in those cases whose life expectancy can be estimated as over three months.

2. More radical measures for therapy, such as freezing, should be reserved for the experimental centers.

3. Patients should be hospitalized for the terminal phase of their disease.

4. Narcotics are not a requisite, or even desirable, in all terminal cases of cancer.

5. Non-narcotic medication should be given a trial for pain control before condemning the patient to a life of dependence on narcotics.

6. Narcotics should be used and their effectiveness judged as analgesics, not hypnotics. The minimal clinically effective analgesic dose of a narcotic may be supplemented by hypnotic doses of a barbiturate if hypnosis is desirable.

7. Addiction may develop in three weeks of narcotic administration.

8. Addiction is to be avoided in the terminal cancer patient because with its development come diminishing returns in analgesia and increasing discomfort due entirely to addiction itself.

9. Through the facilities made available by the Committee on Drug Addiction of the National Research Council, hitherto unknown phenanthrene derivatives have been synthesized and subjected to pharmacologic and clinical investigation. The most promising of these to date is methyl dihydromorphinone.

#### ABSTRACT OF DISCUSSION

DR. DAVID I. MACHT, Baltimore: I agree with Dr. Lee that codeine has little value as an analgesic, and I have shown that the antispasmodic property of papaverine resides in its benzyl nucleus and the narcotic property of morphine in its phenanthrene nucleus (*J. Am. Pharm. A.* **17**:15, 1928). While the numerous compounds described by Small, Himmelsbach, Mosettig and others are marvels of chemical synthesis, they have not yielded a derivative superior to morphine in preventing addiction. Even methyl dihydroxymorphinone, says Dr. Lee, is but a curiosity. I therefore deem it unprofitable to search for other morphine substitutes in the phenanthrene field. Cobra venom, which Dr. Lee mentions, gives more promise as a morphine substitute. Its neurotoxin, while analgesic, is neither protein nor alkaloid but a glucoside (*Ber. d. deutsch. chem. Gesellsch.* **71B**:1302, 1908). My first report (*Proc. Nat. Ac. Sc.* **22**:61, 1936) of 105 cases treated with cobra venom showed that this drug effected some degree of analgesia in 60 per cent of the series. During the last three years the use of cobra venom has increased to such an extent that two thousand boxes are now being consigned monthly to physicians and hospitals. Cobra venom analgesia is localized in the hypothalamus, and the drug neither affects sight or hearing nor depresses the frontal lobes or impairs mental efficiency. Its therapeutic margin of safety is wide, and doses of 5 to 10 mouse units are quite safe. Cobra venom is used to relieve the pains not only of malignant disease but also of neuralgia, arthritis and other chronic pathologic conditions. In therapeutic doses it does not impair kidney and liver function or affect blood morphology and chemistry. Years of clinical experience have revealed that nothing like narcotic addiction follows therapeutic use of cobra venom, which has been substituted largely for morphine as a pain-relieving agent and has also been successfully employed in treatment of a limited number of cases of true narcotic addiction. It is desirable to make an extensive study of cobra venom in the latter condition.

DR. LYNDON E. LEE JR., Wrentham, Mass.: The analgesic synergism Dr. Macht suggests between the isoquinoline group or papaverine and the phenanthrene group or morphine is very low and occurs in only about 50 per cent of people. The predominant effect of the isoquinoline group is the relaxation of smooth muscle as opposed to the contraction initiated by the phenanthrenes. With the administration of the combination, as in the use of opium, one obtains largely antagonistic rather than synergistic effects. It is possible that the apparent analgesic synergism occurs only in those cases in which smooth muscle spasm is a factor in causing pain. Dr. Macht suggests that further chemical and clinical investigation be carried on with substances other than opiates in an attempt to synthesize an analgesic. This is one of the important branches of the

11. Eddy, N. B.: The Search for More Effective Morphine-like Alkaloids, *Am. J. M. Sc.* **197**: 464-479 (April) 1939.

work by the Research Council's Committee on Drug Addiction. Dr. Erich Mosettig has been paralleling Dr. Small's phenanthrene studies with work on dibenzofuran and carbazol, both unrelated to morphine. This work has reached a point at which he can supply some potent analgesics, but these are thus far so toxic in animals that we cannot afford to take them into the clinic for trial. I cannot sympathize with Dr. Macht's explanation of cobra venom as a simple substance. No work on its chemical nature has been published in this country. Hudson is not at all certain that it is a glucoside, and the filtration process of preparation is no guaranty that all protein constituents have been removed. The doses of cobra venom suggested earlier by Dr. Macht are considered to be entirely inadequate. They are tripled and quadrupled by other workers before any effect is noted. With regard to the use of cobra venom in withdrawal, here, as in other departments of study on the material, inadequate and uncontrolled work has been done. Of the one thousand addicts in the Kentucky Public Health Service Hospital and narcotic farm none, so far as I am aware, have attempted the alleviation of withdrawal phenomena by the use of cobra venom. Obviously a rigidly controlled study of this is desirable and no general use of the material should be made in this field until its worth has been proved.

### *Clinical Notes, Suggestions and New Instruments*

#### APPARENT CURE OF A TYPHOID CARRIER WITH SOLUBLE IODOPHTHALEIN

JAMES R. ENRIGHT, M.D., HONOLULU, T. H.  
Director, Bureau of Communicable Diseases

The report of Saphir and Howell<sup>1</sup> describing an apparent cure of a carrier of the typhoid-paratyphoid group by the oral administration of soluble iodophthalein has such potential significance from a public health standpoint that it was considered advisable to record another case in which the administration of the same drug was followed by the disappearance of Eberthella typhi from the stool.

#### REPORT OF CASE

C. B., a man aged 34, a Filipino living at the Hawaiian Homestead, Hoolehua, Molokai, was seen by a physician (P. W.) on the afternoon of Sept. 23, 1937. He gave a history of having felt "sick" since September 8 but he had not gone to bed. He complained of severe headache on September 17 but felt better on the 18th and 19th. On the 20th the symptoms became so severe that he went to bed. He summoned his physician on the 23d. The physician, suspecting typhoid, immediately had the patient hospitalized at the Robert W. Shingle Jr. Memorial Hospital on Molokai, where a stool was taken September 26 and found positive for Eberthella typhi.

All contacts were immunized and stools obtained for culture. No positive stools were found among the contacts, including H. B., the wife of the patient. The date of recovery of this patient is not recorded.

On May 8, 1940, another case of typhoid was discovered. G. P., a man aged 30, a Hawaiian from Kawela, had stool cultures positive for Eberthella typhi.

The usual investigation of contacts disclosed that C. B. and his wife H. B. had moved to this locality and were intimate contacts of G. P. Stools submitted by C. B. were negative but a stool submitted by H. B. on May 25 was found positive for Eberthella typhi. She was admitted to Ualapue Hospital, May 31, by Dr. T. M. for a period of observation. During her stay in the hospital her temperature was normal at all times and all examinations gave essentially negative results except that she was in the seventh month of pregnancy. On May 28, in the course of investigation, she as well as all other contacts had received the first injection of typhoid-paratyphoid

vaccine.<sup>2</sup> She received her second injection June 4 and her final one June 11. She was kept in the hospital throughout the month of June and no symptoms or signs of typhoid developed. Five stool examinations were made during her stay, the laboratory reporting them positive for Eberthella typhi on June 11, 15, 18, 20 and 30. As there is only one bacteriologic laboratory on Molokai, some difficulty had been experienced in the past in obtaining fresh stools for culture. In 1937 the stool specimens submitted were in many cases taken the day previous or many hours before plating could be done. This may have been the reason positive stools were not found at that time. As Havens<sup>3</sup> states that immediate examination, lacking special means of preservation, is necessary to prevent the enormous overgrowth of Bacillus coli, a special effort was made in May and June 1940 to have all specimens submitted for plating within two hours. The stools were plated on eosin-methylene blue agar and bismuth sulfite agar. Suggestive colonies were transferred to Russell's double sugar medium and confirmed by hanging drop examination and agglutination with specific antiserum.

The patient appeared perfectly normal during her stay, showing no symptoms or signs of any illness except for having consistently positive stools. As there is no regulation in the territory requiring isolation of a typhoid carrier, she could not be held in the hospital. The patient grew very restless and wished to return home to take care of her six children. The husband, who was receiving aid through social security, was unable to go to work because he had to take care of the children, although employment was available.

In view of these facts, the patient was given permission to go home, provided she did not act as a food handler and observed proper precautionary measures. This department, in a communication to her physician, referred to the article of Saphir and Howell<sup>1</sup> and suggested that before her discharge from the hospital soluble iodophthalein be given by mouth in the manner described by the authors. Accordingly, 3.5 Gm. of soluble iodophthalein was given by mouth on July 4, followed by 3.5 Gm. on July 8. A stool taken on July 9 was found to be negative for Eberthella typhi. A third dose of 3.5 Gm. was given on July 11 and stools taken on the 12th and 13th were also found to be negative. The patient was discharged from the hospital and returned to her home. She will be followed and a careful check made of stools for a period of at least one year. She will then be classified as carrier free if her stools remain negative.

No conclusions can be drawn from this single case but because of the abrupt disappearance of Eberthella typhi from the stools following the oral administration of soluble iodophthalein it seems that the result in this case parallels Saphir and Howell's result and warrants the trial of this comparatively harmless treatment on carriers of the typhoid-paratyphoid group before surgical treatment is considered. It may also be well to emphasize the value of plating fresh stools in the search for carriers.

#### RELAPSING FEVER: REPORT OF THREE CASES. ONE IN A SIX DAY OLD INFANT

SIDNEY K. MORRISON, M.D., AND LAWRENCE PARSONS, M.D.  
RENO, NEV.

That relapsing fever "has been rarely observed in the United States," as recently stated by Neilson,<sup>1</sup> is not exactly true, particularly as concerns California and Nevada. Endemic foci at Big Bear Lake in the San Bernardino Mountains some 60 miles east of Los Angeles and at Lake Tahoe in the Sierra Nevada Mountains about 50 miles from Reno, Nev., have been known for a number of years. About twelve years ago Dr. Charles W. Bonyngue demonstrated the spirochetes (Borrelia recurrentis) of relapsing fever in blood smears of a patient from Big Bear

2. Lilly's V 765 vaccine was used.

3. Havens, L. C.: The Bacteriology of Typhoid Salmonella and Dysentery Infection and Carrier States, New York, the Commonwealth Fund, 1935, p. 3.

Dr. Karl F. Meyer, Director of the George Williams Hooper Foundation for Medical Research, University of California, San Francisco, gave helpful counsel.

1. Neilson, W. P.: Report of a Case of Relapsing Fever, J. A. M. A. 115:125 (July 13) 1940.

From the Board of Health, Territory of Hawaii.  
1. Saphir, William, and Howell, Katharine M.: Soluble Iodophthalein in Treatment of Carriers of Typhoid-Paratyphoid Group, J. A. M. A. 114:1988 (May 18) 1940.

Lake at one of the monthly meetings of the Los Angeles Pathological Society, and the members present were impressed by the rarity of cases at that time.

Since 1933 we have seen about half a dozen patients with relapsing fever each summer here in Reno, nearly all the patients acquiring the infection at Lake Tahoe, where the strawberry mite (*Ornithodoros hermsi*), a small tick living on the gray tree squirrel, transmits the disease to man. Guttman<sup>2</sup> of Sacramento, Calif., sees about as many cases each summer as we do, and a technician in the laboratory in which one of us (L. P.) is associated states that Dr. Paul W. Christman, another pathologist in Sacramento in whose laboratory she was employed for four years, also sees quite a number of cases each summer vacation period. In most cases these originated at Lake Tahoe.

Recently, however, we have seen three cases occurring in one family who had not been to Lake Tahoe this year. These cases are of interest since one, the newborn infant, may have acquired the infection in utero.

#### REPORT OF CASES

CASE 1.—Mrs. H. G. aged 28, under the care of one of us (S. K. M.), suffered premature rupture of the fetal membranes on May 24, 1940. On the following day she had a severe chill, complained of headache, had a fever of 103 F. and was admitted to St. Mary's Hospital. The blood count on admission showed 68 per cent hemoglobin (14.5 Gm.=100 per cent), 3,750,000 erythrocytes and 7,600 leukocytes, with 85 per cent neutrophils, 18 per cent of which were nonfilament forms. The urine was normal and the Kolmer blood Wassermann reaction was negative. Labor was induced and a female infant weighing 5 pounds 15 ounces (2,693 Gm.) was delivered; it appeared slightly premature.

May 26 the mother again had a severe chill and a temperature of 105 F. The leukocyte count was 8,550 with 83 per cent neutrophils, 20 per cent being nonfilament forms. In view of the apparent absence of puerperal infection, pneumonia or other cause for the chills and fever, the laboratory was asked to examine the patient's blood smears for the spirochetes (*Borrelia recurrentis*) of relapsing fever. A rather extensive experience with this disease in this locality had taught the lesson of suspecting it in otherwise healthy persons with essentially normal leukocyte counts but suffering chills and fever who had recently visited Lake Tahoe. The patient and her husband had not been there for a year, but it was nevertheless thought worth while to attempt to find the spirochetes. Numerous organisms of *Borrelia recurrentis* were found in the blood smears stained with Wright's stain. Neoarsphenamine 0.45 Gm. was given intravenously; the temperature returned to normal within twelve hours and remained so.

CASE 2.—The baby six days after birth suddenly became ill with a fever of 104 F., cyanosis and difficult breathing. The leukocyte count was 7,200, with 61 per cent neutrophils, of which 5 per cent were nonfilament forms. Relapsing fever was suspected and numerous organisms of *Borrelia recurrentis* were found in blood smears, four or five being frequently observed in a single oil immersion field. They were very active and numerous in the dark field examination of a wet preparation of untreated blood. Sulfarsphenamine 0.075 Gm. was given intramuscularly, but since the fever persisted and the spirochetes could still be found in the blood smears after thirty-six hours, 0.10 Gm. more was given. The temperature thereupon returned to normal within twenty-four hours and the baby has remained well.

CASE 3.—M. G., the husband, on June 6, twelve days after his wife had become ill, suddenly had severe chills, headache and a high fever. Organisms of *Borrelia recurrentis* were found in his blood smears. His leukocyte count was 9,500, with 72 per cent neutrophils, 5 per cent being nonfilament forms. Neoarsphenamine was given intravenously and his temperature returned to normal within thirty-six hours.

#### COMMENT

Whether the baby was infected in utero by the passage of the spirochetes in the mother's blood through the placenta or was inoculated by them through the unbroken skin during its transit

in the birth canal, as suggested by Dr. Karl F. Meyer, is an open question. The incubation period would fit either case. No strawberry mites (*Ornithodoros hermsi*) or rodents were found in the trash-littered basement of the home of the parents. Several ticks were found but not of the *Ornithodoros* group. The home was thoroughly fumigated with hydrocyanic acid gas.

#### SUMMARY

1. Relapsing fever is fairly common in California and Nevada during the summer months.
  2. The three cases reported here occurred in the members of one family.
  3. The newborn infant may have been infected by placental transmission or possibly during its passage through the birth canal.
  4. Relapsing fever is suspected in this region in persons taken suddenly ill for no obvious cause, having chills, fever, headache and a normal leukocyte count. Mild leukocytosis is uncommon.
- 15 East First Street.

## Special Article

### GLANDULAR PHYSIOLOGY AND THERAPY

#### DYSFUNCTIONS OF THE ANTERIOR LOBE OF THE PITUITARY AND THEIR TREATMENT

ELMER L. SEVRINGHAUS, M.D.

MADISON, WIS.

*This special article is published under the auspices of the Council on Pharmacy and Chemistry. It is one of a series which will be published in book form as the second edition of "Glandular Physiology and Therapy." The opinions expressed in this article are those of the author and do not necessarily represent the views of the Council.—Ed.*

Among the disturbances of the several functions of the anterior lobe of the pituitary, only two are susceptible to treatment with any assurance of success at present. These are dysfunctions in the supply of the growth-promoting and gonadotropic factors, which will be discussed in detail. Although the thyrotropic extracts of the anterior lobe of the pituitary have been shown to act in some persons, it has not yet been possible to secure sustained stimulation of the thyroid in hypothyroid patients.<sup>1</sup> Neither is there adequate evidence to warrant routine irradiation of the pituitary in an attempt to reduce production of the thyrotropic substance in patients with persistent thyrotoxicosis. The factors involved in pituitary stimulation of the adrenal glands are still further removed from immediate application in human therapy. The dysfunctions known under such terms as "basophilism," "Cushing's syndrome" or "the adrenogenital syndrome" will be discussed in another article of this series.<sup>2</sup> Therapy directed to the pituitary is to be considered in such cases only when a tumor is demonstrable, and then it should consist of hypophysectomy or destructive irradiation. The effects of anterior pituitary extracts on carbohydrate and fat metabolism in experimental animals probably have their counterparts in human clinical situations, but at present the most that can be done is to watch for

From the Wisconsin General Hospital.

1. Thompson, W. O.; Thompson, P. K.; Taylor, S. G., III, and Dickie, L. F. N.: Influence of Pituitary in Thyroid Disease, *West. J. Surg.* 47: 4-9 (Jan.) 1939.

2. Section IV-a of outline for the book "Glandular Physiology and Therapy."

2. Guttman, P. H.: Personal communication to the authors.

evidences of disturbed sugar tolerance in patients with other anterior lobe dysfunctions and for stigmas of pituitary disorders in those who are known to have diabetes mellitus or recurrent severe hypoglycemia.

#### DYSFUNCTION IN SUPPLY OF GROWTH HORMONE

**Gigantism.**—Excessive activity of the anterior lobe of the pituitary in stimulating growth during childhood and early adolescence may so augment the rate of increase in stature that gigantism is produced before the closure of the epiphyses limits further elongation of the long bones. It seems unwise to use irradiation to limit this growth because of the danger of simultaneously interfering with other pituitary functions. Attempts to limit stature should not be undertaken until the child is over 5 feet (152.5 cm.) tall, for an alarmingly fast growth may subside spontaneously as stature approaches the usual adult range. Clinical experience in this field is still meager, but it is possible to observe the maturation of bones with films taken at intervals of six to twelve months and to stimulate maturation in the ossifying process when there is delayed epiphysal union. The physiologic factors which hasten this maturation are thyroid, androgen and estrogen. Occasionally these principles have been used in an attempt to expedite the union of epiphyses, because the effects of such substances on structures other than bone are temporary or are merely additive to the secretion of the glands in the child's body. Such a program is admittedly still experimental, and the dosage cannot be specified. This type of therapy should be undertaken only by a clinician with experience in judging the actions of the substances used.

**Acromegaly.**—When excessive pituitary secretion of the growth-promoting factor occurs after the union of the epiphyses, the bones and soft tissues undergo changes known as acromegaly. If this process is diagnosed while still active, it may be worth attempting to reduce pituitary activity. In cases of acromegaly associated with tumor of the pituitary the choice between surgical removal or irradiation needs to be made. When no neoplasm can be demonstrated, one may hesitate to employ destructive irradiation. Under such circumstances large doses of estrogen have been reported to give at least temporary benefit.<sup>3</sup> It has been supposed that this acts by inhibition of anterior lobe function. Use of testosterone for this purpose has not been reported. Since acromegaly without a tumor is most apt to occur at the climacteric and is frequently associated with increased growth of facial hair in women, testosterone is not recommended for female patients with acromegaly. The duration of active acromegaly is highly variable, and the need for therapy therefore questionable. The common clinical problem is merely the control or stopping of regional symptoms of tumor and headache, which does not involve endocrine therapy. The occurrence of goiter, myxedema, diabetes mellitus, diabetes insipidus or adrenal insufficiency as complications of acromegaly is of importance in understanding pituitary functions. These complications are treated as when they occur under any other circumstances.

**Dwarfism.**—Underactivity of the growth-promoting factor during childhood is the cause of certain types of dwarfism. If no other adequate cause for the retardation of growth can be found, the cause is assumed

to be hypopituitarism. This conclusion is fortified whenever there are any other evidences of a reduction or an alteration of the functions of the same gland. Exact criteria for hypofunction of the anterior lobe in this responsibility are not available. It is therefore probable that application of potent extracts of the pituitary will not be uniformly successful in treating dwarfism. The materials which have been used are aqueous extracts, which contain inert proteins in addition to the desired active substance. The physiologic action is to increase anabolic processes in many tissues, thereby increasing the positive nitrogen balance and increasing the body weight by the laying down of protein-containing tissues, included in which is an increased amount of bone.<sup>4</sup> There is no uniform method for biologic standardization of these growth-promoting extracts, and it is therefore impossible to make any accurate comparison of the relative values of the several commercial brands in use. All are water soluble and act briefly; hence their efficiency in stimulating growth will be greater when they are given in divided doses at short intervals (daily) than when they are used in similar total amounts at longer intervals (alternate days to weekly). The manufacturers of some of these products suggest interrupted periods of injection, as if to avoid antihormone formation. This interruption is not necessary. It has been frequently suggested that growth will be more rapid if the injection of pituitary extract is augmented by feeding thyroid. This has been demonstrated in animals.<sup>5</sup> Caution is enjoined at this point, for promotion of growth is often undertaken as a late attempt to achieve normal stature before the epiphyses close, and thyroid therapy will certainly tend to expedite the maturing of the skeleton, which includes the union of epiphyses. It is therefore advised that except under most careful observation of the bones thyroid be avoided in treating dwarfism with pituitary extracts, unless there is evidence of hypothyroidism. Therapy for dwarfism should be continued for a minimum of three months to detect the beginning of results before it is abandoned as of no avail. When growth response is secured, the injections should be pursued until the stature is that desired for the age or until no gain is secured for at least three months and films of the femur show the epiphyses to be firmly united.

**Pituitary Cachexia.**—The failure of the anterior lobe of the pituitary to secrete the growth factor in adult life has not yet been definitely associated with any syndrome. It is usually assumed that pituitary cachexia (Simmonds' disease) is the consequence of a complete failure of the anterior lobe, with failure of all pituitary functions. The diagnostic confusion between anorexia nervosa and pituitary cachexia makes antemortem diagnosis uncertain. The reported results of the treatment of patients for these conditions are conflicting.<sup>6</sup> Benefits have been claimed for the use of various types of pituitary extracts and placental extracts, for other endocrine therapy, and for improvement of nutrition as well as for psychotherapy. Until the diagnostic riddle can be solved, therapy will remain uncertain. It is noteworthy that those who claim the best results

3. Kirklin, O. L., and Wilder, R. M.: Follicular Hormone Administration in Acromegaly, Proc. Staff Meet., Mayo Clin. 11: 121-125 (Feb. 19) 1936.

4. Lee, M. O., and Schaffer, N. K.: Anterior Pituitary Growth Hormone and the Composition of Growth, J. Nutrition 7: 337-363 (March) 1934.

5. Smith, P. E.: Increased Skeletal Effects in Anterior Pituitary Growth-Hormone Injection by Administration of Thyroid in Hypophysectomized Thyroparathyroidectomized Rats, Proc. Soc. Exper. Biol. & Med. 30: 1252 (June) 1933.

6. Dick, G. F., and Dine, W. D.: Pituitary Extract in Simmonds' Disease, Endocrinology 22: 703-707 (June) 1938. Richardson, H. E.: Simmonds' Disease and Anorexia Nervosa, Arch. Int. Med. 63: 1-5 (Jan.) 1939.



for psychotherapy and improved nutrition admit that some patients may regain normal weight and be socially rehabilitated but still show amenorrhea or other evidences of great reduction in gonadal function. This leaves presumptive evidence of pituitary hypofunction. Therefore the recent attempts to use endocrine therapy for pituitary cachexia have included administration of such diverse materials as growth-promoting pituitary extracts, gonadotropic substances, adrenal cortex extracts and desiccated thyroid. Obviously this, again, is an experimental field, in which dependable results cannot yet be expected.

#### DYSFUNCTION IN SUPPLY OF GONADOTROPIC HORMONES

*Hypersecretion.*—The only condition associated with excessive amounts of anterior pituitary gonadotropic hormones is the climacteric, whether occurring spontaneously or as the consequence of surgical ablation or irradiation of the gonads. There is no evidence that the occurrence of increased amounts of the gonadotropic hormones in the pituitary,<sup>7</sup> the blood or the urine<sup>8</sup> of such patients has any significance for the comfort or health of the patients. It was formerly thought that the relief from typical autonomic disturbances of the climacteric depended on the inhibition of this increased anterior lobe secretion.<sup>9</sup> It has been shown that such inhibition does not occur following the administration of doses of estrogen which provide relief<sup>10</sup> and that complete alleviation of the symptoms is totally unrelated to the presence of the typical climacteric level of gonadotropic substances in the urine. Therefore it is suggested that there is no clinical reason to attempt treatment of hypersecretion of the anterior pituitary gonadotropic hormones as such.

*Hypogonadism in the Male.*—The discussion of testicular disorders in another chapter<sup>11</sup> provides details which need not be repeated. There are three fundamental types: infantilism, adiposogenital dystrophy and cryptorchism. Infantilism is the simple failure of testes to develop, and the therapy is commonly the use of gonadotropic substances. Adiposogenital dystrophy includes in addition to infantilism evident obesity, which is frequently but not always most marked about the lower part of the torso and the trochanteric region. The therapy required here is appropriate dietary reduction of weight plus a gonadotropic substance. In a few cases the reduction of weight has sufficed without endocrine therapy. This may mean that the adolescent development was delayed but eventually appeared, or it may indicate that the reduction in weight achieved some favorable alteration in the endocrine situation. The latter suggestion is entirely hypothetical. Obesity accentuated about the lower part of the abdomen and the trochanteric region but without hypogonadism is not justification for a diagnosis of adiposogenital dystrophy. Such obesity deserves treatment by dietary limitation and exercise but not by use of gonadotropic substances. Cryptorchism may be due to anatomic barriers to testicular descent, in which case the only endocrine problem is

the reduced activity of a testicle which is not in the scrotum. That problem is dealt with elsewhere.<sup>11</sup> There are numerous cases in which delayed descent is associated with infantilism or with adiposogenital dystrophy. It is especially these patients who may benefit from endocrine therapy with the double purpose of accomplishing descent and stimulating development.

As explained by Engel,<sup>12</sup> there are three fundamentally different types of gonadotropic substances available for therapy: anterior pituitary extracts, concentrates from the serum of pregnant mares and concentrates from the urine of pregnant women. The last of these was the first to be used clinically, and it is still recognized as a potent stimulator of the interstitial tissue of the testicle, in response to which the testicle enlarges, the production of testosterone is increased, secondary sex characters are intensified, the genitalia are enlarged, and cryptorchid testes descend unless there is an anatomic barrier. Consequently there have been numerous reports of treatment of cryptorchism with this chorionic gonadotropin. The limitations of this method are discussed by Thompson and Heckel.<sup>13</sup> The dosage employed by them and by Zelson<sup>14</sup> is from 100 to 1,000 units administered from three to seven times weekly. Positive results are to be expected in three months or less. The therapy should be watched carefully to avoid producing genitalia larger than normal for the age. The procedure is more frequently successful with bilateral cryptorchism, in the presence of other evidences of endocrine deficiency and before the age of 15. One great merit of such treatment is that it secures descent in that group of boys who do not require surgical treatment and, by failures, marks out for surgical intervention at an early age those who will require it.

Observations on boys treated with chorionic gonadotropin have led to the conviction that this substance does not stimulate all testicular functions. Spermatogenic tissue shows little response. Animal experiments show that anterior pituitary extracts or concentrates from the serum of pregnant mares will stimulate both interstitial and spermatogenic tissues. Therefore I consider it wiser to treat infantilism over long periods of time with one of these two gonadotropic materials, both of which are now available commercially. There is as yet no agreement about the methods of standardizing anterior pituitary gonadotropic extracts; hence the manufacturers' recommendations as to dosage will vary. The pregnant mare serum extracts will all appear in terms of an international unit during 1940, and the dosages will probably vary from 50 to 300 units given daily or on alternate days. Since these substances are water soluble, act quickly and for brief periods, they should be given at short intervals for maximum effect per unit. Since there is no recognized cycle of testicular growth or activity, these treatments may well be pursued without interruption until results are achieved. So little has been reported about the results of such treatment that prediction of the probable degree of success is uncertain.

*Hypogonadism in the Female.*—The discussion of ovarian dysfunctions and their treatment by Fluhmann<sup>15</sup> includes the varieties of underactivity of the

7. Witschi, E., and Riley, G. M.: Quantitative Studies on the Hormones of Human Pituitaries, *Endocrinology* 26: 565-576 (April) 1940.

8. Fluhmann, C. F.: Anterior Pituitary Hormone in Blood of Women: Preliminary Clinical Classification of Results in Non-Pregnant Individuals, *Endocrinology* 15: 177-183 (May-June) 1931.

9. Jaffecoat, T. N. F.: Estrogenic Hormone Therapy, *Brit. M. J.* 2: 671-676 (Sept. 30) 1939. Sevringhaus, E. L.: *Endocrine Therapy in General Practice*, Chicago, The Year Book Publishers, Inc., 1938, pp. 155-156.

10. Heller, C. G., and Heller, E. J.: Gonadotropic Hormone: Urine Assays of Normally Cycling, Menopausal, Castrated, and Estrin Treated Human Females, *J. Clin. Investigation* 18: 171-178 (March) 1938.

11. Section II, B, 1 and 2 of outline for book "Glandular Physiology and Therapy."

12. Section I, 6 of outline for book "Glandular Physiology and Therapy."

13. Thompson, W. O., and Heckel, N. J.: Undescended Testes: Present Status of Glandular Treatment, *J. A. M. A.* 112: 397-403 (Feb. 4) 1939.

14. Zelson, C.: Treatment of Cryptorchidism with Gonadotropic Substance, *J. Pediat.* 13: 452-461 (April) 1939.

15. Fluhmann, C. F.: Ovarian Dysfunctions and Their Treatment, Section II, A, 6 of outline for book "Glandular Physiology and Therapy."

ovaries, their diagnosis and their therapy. When there is no evidence of primary disorder in the ovaries or of obvious disturbance from some other morbid process in the body, these ovarian hypofunctions are assumed to be a result of hypofunction of the anterior lobe of the pituitary in secreting gonadotropic hormones. Exact proof of this relation awaits far more study by hormone assays than is yet possible. The variety of clinical expressions of hypofunction is not surprising when one considers the three ovarian functions of ovulation, production of estrogen and production of progesterone, the last two of which may vary widely in intensity or duration. Further variables are the time and intensity of secretion of the two anterior pituitary gonadotropic hormones—the follicle-stimulating and the luteinizing hormone. That there is interaction of pituitary hormones on the ovaries and of ovarian hormones on the pituitary cannot be doubted. Knowledge of the quantitative relationships is essential to any completely rational therapy, as well as to diagnosis. At present endocrinologists have only the roughest ideas about these exact processes. Therefore therapy with gonadotropic materials is still crude.

The earliest therapy was with chorionic gonadotropin, but those who were previously enthusiastic have come to realize that the substance produced during pregnancy by chorionic tissue does not stimulate the ovaries of nonpregnant women to develop, to ovulate or to secrete more estrogen.<sup>16</sup> Stimulation of these functions has, however, followed the use of anterior pituitary extracts and concentrates from the serum of pregnant mares. Therefore these materials appear to be the only appropriate ones with which to stimulate hypofunctioning human ovaries. Chorionic gonadotropin is apparently a factor in sustaining the function of the corpus luteum during the first trimester of pregnancy, yet, curiously, there have been no systematic studies of the effect of this substance in the treatment of repeated abortion. This most obvious use of the chorionic gonadotropin might well be explored by gynecologists and obstetricians.

In recent years repeated abortion has been treated chiefly by the employment of progesterone. Although the gonadotropin in pregnant mare serum is probably chorionic in origin, it simulates anterior pituitary gonadotropin very closely. It is not yet justifiable to assume that mare serum concentrate provides a complete substitute in replacement therapy for human hypopituitarism.

In treating girls or women whose ovaries are to be stimulated, it is recommended<sup>17</sup> that small or moderate amounts be administered hypodermically at intervals of one or two days and that each course of injections be not longer than two weeks. The optimum time for such a course is the first two weeks of the menstrual cycle, when the development of a new follicle and growth of a new ovum normally occur. Interruption of the series of doses is advised to avoid continuous stimulation with small amounts of gonadotropin, which is believed to be the cause of polycystic ovaries. In those women who are amenorrheic or whose menses occur at longer intervals than two months without treatment, it may be wise to repeat such a course of pituitary injections, beginning every three weeks, until some semblance of

cyclic function is established. The gage of success in such a program may be symptomatic improvement, restoration of more regular menstrual cycles, improved fertility or evidence of improvement in the endometrium or in the vaginal mucosa. Both diagnosis and therapy are rendered far more certain when treatment is preceded by biopsy of the endometrium<sup>18</sup> and study of stained smears of desquamated epithelium from the vagina.<sup>19</sup> A detailed study of each case is essential to early determination of the probable success of treatment.<sup>20</sup>

The frequency of anovulatory menstruation as a cause of irregularity of cycles, reduced fertility and glandular cystic hyperplasia of the endometrium has led to efforts to stimulate the ovaries to ovulation. The results of Hisaw and co-workers<sup>21</sup> suggested that this was to be accomplished by intravenous injection of a mixture of follicle-stimulating and luteinizing anterior pituitary extracts followed for several days by sustained hypodermic use of the same materials to stimulate secretion by the corpus luteum. This procedure has been tried by several investigators,<sup>22</sup> and a complete program of therapy has been reported by Siegler and Fein<sup>23</sup> with some promise of success. The most acceptable material is the concentrate of pregnant mare serum, which is given in doses of 100 to 300 international units hypodermically for several days to stimulate follicle development, followed by a single intravenous dose of 1,000 to 1,500 units to initiate ovulation, and then by four to six days more of hypodermic therapy to sustain function in the corpus luteum if ovulation occurs.

Since endocrinologists have no knowledge of the amount of gonadotropic hormone produced by the anterior lobe of the pituitary during health, they cannot tell how much is required for replacement therapy in deficiencies. Clinical results certainly indicate that even with the most potent commercial extracts 1.0 cc. daily cannot be regarded as a complete replacement for the secretion of the anterior lobe of the human pituitary. Owing to local reactions to the protein content of even the best preparations and to the cost of therapy, such treatment cannot be expected to be helpful save in the relief of partial deficiencies. If hypopituitarism resembles in chronicity hypothyroidism, diabetes mellitus or hypofunction of the adrenal cortex—a reasonable supposition in many ways—one must expect to use anterior lobe replacement therapy for months or years, not for just a few days. The paucity of cases in which gonadotropic therapy has been attended by striking success should not cause the clinician to doubt the ultimate importance of such treatment, although he may well decide to wait for better diagnostic methods, more potent and less expensive extracts and reports of longer periods of observation of patients now under treatment. Gonadotropic therapy is still in the experimental stage.

18. Campbell, R. E.; Lendrum, F. C., and Sevringhaus, E. L.: Endometrial Histology and Pathology as Revealed by Biopsy Method, *Surg., Gynec. & Obst.* 63:724-731 (Dec.) 1936.

19. Papanicolaou, G. N., and Shorr, Ephraim: Action of Ovarian Follicular Hormone in the Menopause, as Indicated by Vaginal Smears, *Am. J. Obst. & Gynec.* 31:806-831 (May) 1936. Geist, S. H., and Salmon, U. J.: Evaluation of Human Vaginal Smear in Relationship to Histology of the Vaginal Mucosa, *ibid.* 38:392-399 (Sept.) 1939. Sevringhaus, E. L.: Treatment of Gonadal Hypofunction, *Bull. New York Acad. Med.* 16:53-82 (Feb.) 1940.

20. Sevringhaus, E. L., and Campbell, R. E.: Endocrinopathic Amenorrhea: Causes and Treatment, *Am. J. Surg.* 48:197-204 (April) 1940.

21. Hisaw, F. L.: Physiology of Menstruation in Macacus Rhesus Monkeys, *Am. J. Obst. & Gynec.* 29:638 (May) 1935.

22. Davis, M. E., and Koff, A. K.: Experimental Production of Ovulation in Human Subjects, *Am. J. Obst. & Gynec.* 36:183-189 (Aug.) 1939.

23. Siegler, S. L., and Fein, M. J.: Studies in Artificial Ovulation with the Hormone of Pregnant Mares' Serum, *Am. J. Obst. & Gynec.* 38:1021-1036 (Dec.) 1939.

16. The Present Status of Therapy with Chorionic Gonadotropin, report of the Council on Pharmacy and Chemistry, *J. A. M. A.* 114:487-489 (Feb. 10) 1940.

17. Campbell, R. E., and Sevringhaus, E. L.: Pituitary Gonadotropic Extracts for Treatment of Amenorrhea, Menorrhagia, and Sterility, *Am. J. Obst. & Gynec.* 37:913-928 (June) 1939.

## SUPPLY OF MAMMATROPIC HORMONE

The use of anterior pituitary extracts which are known to stimulate lactation by well developed mammary glands has not proved dependably successful in human subjects.<sup>24</sup> Details of experimental work on this problem are discussed in another chapter.<sup>25</sup> There is reason to hope for progress in this field of therapy. Better results have been achieved in the use of estrogens to prevent or interrupt lactation when clinical indications make this step advisable. For this purpose the patient is treated with high doses of estrogen, given intramuscularly, and the therapy should be successful within one to three days; if it is not, it should be stopped. Dosages have been reported as from 1 to 10 mg. of estrone (theelin) or estradiol benzoate per day. After the first few days there appears to be no need for further therapy. This suggests that the mammatropic hormone secretion which initiates lactation post partum is quickly reduced by therapy to a level which is ineffective in continuing secretion by the breasts. Success has been reported following oral use of 10,000 rat units of estradiol daily in divided doses for from one to four days.<sup>26</sup> The injection of testosterone propionate, 10 to 25 mg., twice daily for one or two days has also been found successful.<sup>27</sup> These methods do not require any additional application of local therapy to the breasts, nor do they cause complications or pain. It is believed that these varied types of endocrine therapy for suppression of lactation operate by inhibition of the secretion of the mammatropic hormone by the anterior lobe of the pituitary.

---

**Council on Physical Therapy**

---

THE COUNCIL ON PHYSICAL THERAPY HAS AUTHORIZED PUBLICATION OF THE FOLLOWING ARTICLE.      HOWARD A. CARTER, Secretary.

---

**RADIOTHERAPY FOR INFLAMMATORY CONDITIONS**

---

ARTHUR U. DESJARDINS, M.D.  
ROCHESTER, MINN.

The treatment of inflammatory processes with roentgen rays is far from new. Indeed, it goes back to about 1900. The earliest mention of the subject is to be found in papers by Freund,<sup>1</sup> Albers-Schönberg,<sup>2</sup> Gautier,<sup>3</sup> Rudis-Jicinsky<sup>4</sup> and Pusey,<sup>5</sup> and in the books of Williams<sup>6</sup> and Belot.<sup>7</sup> An interesting point is that some of the earliest therapeutic trials were made in this

country, but they received no attention until the successful results had been repeatedly confirmed by others here and abroad.

Many physicians are unaware of the favorable influence of roentgen rays or radium on various forms of acute or chronic inflammation. Yet the therapeutic value of irradiation in inflammations has been thoroughly substantiated, and the testimony is so generally favorable that one wonders why it is not used more than it is or why, in many cases, it is employed only after other therapeutic measures have failed to yield the desired results. Perhaps the very multiplicity of inflammatory lesions for which radiotherapy has been claimed to be effective has led to a natural skepticism. Also the many explanations which have been advanced to account for the favorable action of roentgen rays or radium on inflammations have probably led many physicians to discredit the evidence or to ascribe the favorable reports to enthusiasm or to psychic factors. Indeed, without a convincing explanation it would be difficult to believe that the same agent could be therapeutically effective against so many different forms of inflammation. And yet the reason appears to be simple and to rest on abundant experimental evidence.

Others who have heard or read of the therapeutic possibilities of irradiation in inflammatory processes hesitate to make use of the method because they fear deleterious effects on the skin or gastrointestinal disturbances such as are observed in connection with the treatment of malignant tumors. When treating neoplasms the aim is to deliver the largest dose compatible with the integrity of the surrounding tissues. When treating inflammatory lesions, on the contrary, only small or moderate doses are employed. Doses that might strain the tolerance of the skin are unnecessary and should be avoided as potentially dangerous. For acute inflammations, especially, the doses required are so small that the skin or the gastrointestinal tract cannot be affected.

**ACUTE INFLAMMATION**

Many varieties of acute inflammation yield rapidly to a small dose of roentgen rays. By a small dose is meant one representing less than half the tolerance dose of the skin; a dose as small as a fourth of the so-called erythema dose, or even less, is often sufficient, but this may vary somewhat according to the character and stage of the lesion in a given case. A significant point is that the more acute the inflammation, the smaller is the dose of rays required. With such small doses there can be no question of cutaneous or systemic reaction; therefore, weak and febrile patients can be treated without danger. In most cases a single exposure is sufficient, but occasionally it may be advisable to repeat the treatment a few days later. This is particularly true when the initial dose has been exceptionally small or when the region treated has not been wide enough.

Among the acute inflammatory conditions in which the therapeutic value of irradiation has been established are furuncle, carbuncle, abscess, cellulitis and phlegmon, onychia and paronychia, acute adenitis, pneumonia, acute parotitis and erysipelas. In other forms of acute inflammation, such as sinusitis, otitis and mastoiditis, pelvic infection, osteomyelitis and gas bacillus infection, an increasing body of evidence indicates an equally favorable response in many cases.

24. Stewart, H. L., Jr., and Pratt, J. D.: Effect of Prolactin on Mammary Gland Secretion, *Endocrinology* 25: 347-353 (Sept.) 1939.

25. Section I, 5 of outline for book "Glandular Physiology and Therapy."

26. Foss, G. L., and Phillips, P.: Suppression of Lactation by Oral Estrogen Therapy, *Brit. M. J.* 2: 887-890 (Oct. 29) 1938.

27. Kurzrok, Raphael, and O'Connell, C. P.: Inhibition of Lactation During Puerperium by Testosterone Propionate, *Endocrinology* 23: 476-478 (Oct.) 1938.

From the Section on Therapeutic Radiology, the Mayo Clinic.

1. Freund, L.: Ein mit Röntgen-Strahlen behandelter Fall von Naevus pigmentosus piliferus, *Wien. med. Wchnschr.* 47: 428-434, 1897.

2. Albers-Schönberg: Beitrag zur therapeutischen Verwendung der Röntgenstrahlen in der Behandlung des Lupus, *Fortschr. a. d. Geb. d. Röntgenstrahlen* 1: 72-75, 1897-1898.

3. Gautier: Traitement de l'acné et de la couperose par les rayons X, *Cong. internat. de méd.* 4: 385, sect. 8, 1899.

4. Rudis-Jicinsky, J.: Lupus Treated by X-Rays, *Am. X-ray J.*, 1898, p. 423.

5. Pusey, W. A.: Lupus Healed with Roentgen Rays: Report of Case, *J. A. M. A.* 35: 1476-1478 (Dec. 8) 1900.

6. Williams, F. H.: The Roentgen Rays in Medicine and Surgery as an Aid in Diagnosis and as a Therapeutic Agent; Designed for the Use of Practitioners and Students, New York, Macmillan Company, 1903.

7. Belot, Joseph: La radiothérapie, son application aux affections cutanées, Paris, 1904, No. 426.

**Pyogenic Infection.**—When irradiated early, during the stage of maximal leukocytic infiltration, many lesions due to pyogenic cocci do not suppurate; their evolution is arrested and they undergo spontaneous resolution. Therefore, the treatment is most effective when other methods of treatment are least effective; it is painless and does not interfere with the activities of the patient. Pain is often relieved in a few hours, but sometimes the relief may be preceded by exacerbation for a brief period. Hot or other dressings are often unnecessary, or the period during which they must be applied is shortened. Treatment after suppuration has set in tends to hasten the suppurative process, the duration of which may thus be more or less diminished. Hence the patients should be kept under close observation so that, if necessary, the surgeon may provide adequate drainage at the proper time. But acute pyogenic inflammations do not always respond so favorably; in a minor proportion of cases they yield little or not at all. This is especially true when the treatment is started long after the onset, that is, late in the course of the inflammation, when exudates have undergone organization and when some degree of connective tissue proliferation has occurred.

**Pneumonia.**—As early as 1905 and 1906 Musser and Edsall<sup>8</sup> and Edsall and Pemberton<sup>9</sup> observed and reported the strikingly favorable influence of a small dose of roentgen rays in four cases of delayed resolution of lobar pneumonia. Every other therapeutic measure having failed to improve the pulmonary condition of the patients, roentgen irradiation was tried as a last resort. Within twenty-four hours after exposure, resolution of the pneumonic exudate set in and proceeded rapidly, and the patients recovered. These observations were subsequently confirmed by A. J. and W. A. Quimby<sup>10</sup> and by Krost<sup>11</sup> and Torrey.<sup>12</sup> In fact, the Quimbys were so impressed by the rapid influence of irradiation in ten cases that they were impelled to testify that "no pathologic process in the body responds quicker to an x-ray exposure than the nonresolution following pneumonia." Since then Heidenhain and Fried,<sup>13</sup> Holzknecht,<sup>14</sup> Merritt and McPeak<sup>15</sup> and others have observed favorable action of roentgen rays on postoperative pneumonia as well as on pneumonia unrelated to surgical intervention, in a large percentage of cases in which the treatment was employed. Naturally the best results are to be obtained from early treatment. As pointed out by Musser and Edsall, irradiation cannot be expected to have much effect once the pneumonic inflammation has become organized or when the treatment is given shortly before impending death.

**Acute Parotitis.**—Every surgeon is aware of the sinister character of that form of acute parotitis which

arises as a complication of certain operations, especially those on the large intestine, and of the high mortality associated with it. The first record of the favorable effect of irradiation on this disease appears to have been made by Heidenhain,<sup>16</sup> who found that the inflammation reacted much as do other acute inflammatory processes. Rankin and Palmer<sup>17</sup> found that a moderate dose of radium, applied soon after the onset, caused the inflammation to subside in most cases within twenty-four to forty-eight hours. Moreover, suppuration usually did not occur and the mortality was correspondingly reduced. Radium is sometimes preferable because the treatment can thus be given without disturbing the patient. When portable roentgen therapeutic apparatus is available, however, treatment with roentgen rays is preferable because the necessary dose can be given in much less time than with radium.

**Erysipelas.**—When erysipelas does not complicate diabetes or nephritis, roentgen irradiation is usually followed by prompt abatement of the fever and recession of the lesions. This is especially true when the patients are adults and when the treatment is given early. In children, for some unknown reason, the disease does not respond quite so well. In some cases, after an initial period of improvement the inflammation may again become active and additional treatment may be required to arrest the process. When this happens it is usually because the initial treatment was confined too closely to the apparent limits of visible involvement. Too much stress cannot be laid on the importance of including in the field of irradiation a wide zone of apparently normal tissue around the lesion. A single dose, corresponding to 100 or 200 roentgens of roentgen rays, generated at 130 or 140 kilovolts and filtered through 4 mm. of aluminum, is usually sufficient.

Favorable results may also be obtained by exposing the affected region to an erythema or blistering dose of ultraviolet rays. A possible disadvantage is that during the period of cutaneous reaction to treatment it may be difficult to know what is disease and what represents reaction. Roentgen irradiation has no such disadvantage; the dose required does not cause reactive inflammation.

**Other Acute Inflammations.**—Other acute inflammations have been found to yield equally well to roentgen irradiation. Among these may be mentioned acute otitis and acute sinusitis. Some years ago Granger<sup>18</sup> reported that in certain cases of acute mastoiditis in which the mastoid region had been exposed to small doses of roentgen rays for diagnostic purposes the inflammation had subsided and an operation had been unnecessary. Other favorable reports have appeared since then. Acute osteomyelitis also has been found to respond favorably. As in other acute inflammations, the best results have been obtained when the lesions were treated early.

In 1936 Kelly and Dowell<sup>19</sup> reported that favorable results had been obtained in cases of gas bacillus infection. Since then these authors have published several additional reports based on a larger number of

8. Musser, J. H., and Edsall, D. L.: A Study of Metabolism in Leukemia Under the Influence of the X-Rays with a Consideration of the Manner of Action of the X-Rays and of Some Precautions Desirable in Therapeutic Use, *Tr. A. Am. Physicians* 20: 294-323, 1905.

9. Edsall, D. L., and Pemberton, Ralph: The Use of the X-Rays in Unresolved Pneumonia, *Am. J. M. Sc.* 133: 286-297 (Feb.) 1907.

10. Quimby, A. J., and Quimby, W. A.: Unresolved Pneumonia: Successful Treatment by Roentgen Ray, *New York State J. Med.* 103: 681-683 (April 8) 1916.

11. Krost, G. N.: Unresolved Pneumonia in Children: Treatment with Roentgen Rays, *Am. J. Dis. Child.* 30: 57-71 (July) 1925.

12. Torrey, R. G.: Roentgenotherapy in Disorders of the Respiratory Tract, Particularly Those Associated with Enlargement or Persistence of the Thymus Gland, and Those Associated with Unresolved Pneumonic Exudates, *S. Clin. North America* 7: 221-235 (Feb.) 1927.

13. Heidenhain, Lothar, and Fried, Carl: Röntgenbestrahlung und Entzündung, *Arch. f. klin. Chir.* 133: 624-655 (April) 1924; *Klin. Wchnschr.* 3: 1121-1122 (June 17) 1924.

14. Holzknecht, Guido: Roentgen Treatment of Spontaneous Post-traumatic and Postoperative Coccus Infections and Suppurations, *Am. J. Roentgenol.* 15: 332-336 (April) 1926.

15. Merritt, E. A., and McPeak, E. M.: Roentgen Irradiation in Unresolved Pneumonia, *Am. J. Roentgenol.* 23: 45-48 (Jan.) 1930.

16. Heidenhain, Lothar: Röntgenbestrahlung und Entzündung, *Strahlen-therapie* 24: 37-51, 1926.

17. Rankin, F. W., and Palmer, B. M.: Postoperative Parotiditis: Treatment Without and With Radium, *Ann. Surg.* 92: 1007-1013 (Dec.) 1930.

18. Granger, Amédée: The Treatment of Infections of the Mastoids of Infants, When There Is No Sign of Destruction Present, with Fractional Doses of the Roentgen Rays, *New Orleans M. & S. J.* 84: 111-113 (Aug.) 1931.

19. Kelly, J. F., and Dowell, D. A.: Present Status of the X-Ray as an Aid in the Treatment of Gas Gangrene, *J. A. M. A.* 107: 1114-1118 (Oct. 3) 1936.

cases. According to them the only patients who died were those in whom an affected extremity had been amputated. The number of cases included in their latest report is now sufficient to command attention, especially since they appear to have succeeded in reducing the mortality to less than 10 per cent when amputation was necessary and to less than 5 per cent when it was not.<sup>20</sup> If the experience of others should confirm the results obtained by Kelly and Dowell, roentgen therapy might be shown to be a great boon to patients afflicted with this virulent form of infection.

In treating inflammations caused by such virulent bacteria, Kelly and Dowell have found it advantageous to use doses as small as 100 roentgens and to repeat them daily or twice daily for three or four days. Although the reason why this procedure is more effective is not clear, it is possible that when the infecting bacteria have a high degree of virulence a single irradiation does not influence a sufficient number of circulating leukocytes to overcome the infection. But when irradiation is repeated daily or twice a day for three or four days, the number of leukocytes acted on by the rays must necessarily be much greater, and this may account for the greater efficacy of this method in the treatment of gas bacillus infection. As streptococcal infections often assume a virulent form and leukocytic infiltration is often slight or wholly lacking, it is possible that the same method of small doses repeated daily or twice daily for three or four days would have a similar advantage.

#### CHRONIC INFLAMMATIONS

For years it has been known that many forms of chronic inflammation are favorably influenced by roentgen irradiation. Among these may be mentioned numerous varieties of chronic inflammation of the skin in which the therapeutic value of radiotherapy is conceded by experienced dermatologists. Other chronic inflammatory processes which may be cited are tuberculous adenitis, peritonitis, keratitis and iritis, actinomycosis and blastomycosis, trachoma in its early stages, and active infectious arthritis. Two factors which influence the effect of irradiation are that the dose of roentgen rays must be larger than that used for acute inflammations and that treatment must be repeated at intervals for some time. By a larger dose is meant a dose varying between 50 and 80 per cent of the tolerance dose when given at one time or, in international units, between 300 and 500 roentgens, according to the conditions of irradiation. Rays generated at 120 or 140 kilovolts and filtered through 4 or 6 mm. of aluminum are usually adequate. Rays generated at higher potentials can be used with approximately equal effect. For skin diseases, unfiltered rays or rays filtered through 2 mm. of aluminum and generated at 80 or 100 kilovolts are generally preferable. The treatment of chronic inflammatory lesions with maximal (erythema, tolerance or tumor) doses is bad practice and should be avoided as potentially dangerous. Since treatment must be repeated at intervals for varying periods, the use of maximal doses may lead to undesirable effects or, by superimposing a reactive inflammation, may cause the original inflammation to spread rather than to abate.

*Tuberculous Processes.*—Although considerable variation may be observed in different cases, the effect of irradiation on tuberculous processes is characteristically

slow. In tuberculous adenitis the affected region must be irradiated every three or four weeks for from three to twelve months. When calcification is absent, the inflamed nodes gradually recede and may disappear completely or may remain as small fibrous granules. Unless abundant, caseous material may be absorbed or may be replaced by calcium. When suppuration occurs drainage may be advisable, but sometimes the pus can be withdrawn through a needle of large bore, which should be introduced not through the thinnest part of the fluctuant region but to one side through more substantial tissue, so as to avoid the formation of a sinus. The extensive surgical procedures formerly in vogue are now seldom necessary. The resolution of tuberculous lesions appears to be hastened by supplementing periodic roentgen irradiation with daily exposure of the entire body to graduated doses of sunlight or to ultraviolet rays generated artificially. Ultraviolet irradiation confined to the affected region is usually a waste of time.

Much the same may be said of tuberculous peritonitis. An important consideration is that the entire abdominal cavity should be irradiated as uniformly as possible. This can best be done by dividing the anterior half of the abdomen from the level of the diaphragm to that of the pubic region into four fields, with the navel as the common center; the posterior half should be divided into four corresponding fields.

Radiotherapy is also an effective method of treating tuberculosis of the cornea or iris. The lesions recede more rapidly after exposure to roentgen rays than do similar lesions in other parts of the body. The dose of roentgen rays should never exceed three fourths of a minimal erythema dose; a larger dose, especially for children, may lead to epithelial degeneration of the crystalline lens and to cataract formation.

*Actinomycosis; Blastomycosis.*—When actinomycosis affects the face, mouth or other superficial structures, roentgen or radium irradiation, supplemented by the internal use of large doses of iodides and sometimes by simple surgical drainage of an abscess, is the most effective therapeutic measure, and a large proportion of patients can thus be permanently cured.

Not infrequently, actinomycotic inflammation arises in the intestine, especially the lower part of the small intestine, where it is often mistaken for simple or suppurative appendicitis. In many cases one or more operations are performed and the true character of the process is not recognized. This is unfortunate because, if the lesion is actinomycotic in character, exploratory maneuvers or any measures beyond simple drainage of an abscess serve only to spread the infection. Thorough exposure of the entire abdomen (front and back) to about three fourths of an erythema dose of roentgen rays, repeated every three or four weeks, may be followed by substantial improvement and sometimes by complete and permanent cure. But when the infection has extended to the respiratory tract (bronchi, lungs and pleura), more than slight and temporary improvement is not likely to be obtained with any method of treatment.

*Trachoma.*—Trachoma is characterized by conjunctival granulations composed largely of lymphocytes. These granulations are gradually replaced by connective tissue, and the eyelids become sclerosed and distorted. As early as 1902 and 1903, Mayou,<sup>21</sup> Stephenson and

20. Kelly, J. F.; Dowell, D. A.; Russum, B. C., and Colien, F. E.; *The Practical and Experimental Aspects of the Roentgen Treatment of Bacillus Welchii (Gas Gangrene) and Other Gas-Forming Infections*, Radiology 31: 608-619 (Nov.) 1938.

21. Mayou, Stephen: A Case of Trachoma Treated by X-Rays, Tr. Ophth. Soc. U. Kingdom 22: 95-96, 1902; *The Treatment of Trachoma by the X-Rays*, ibid. 23: 10-23, 1903.

Walsh<sup>22</sup> and Cassidy and Rayne<sup>23</sup> made the discovery that, in some cases, the trachomatous granulations receded after exposure to roentgen rays and that the patients were cured. Subsequently Thielemann,<sup>24</sup> Cochard<sup>25</sup> and Meldolesi and Sabbadini<sup>26</sup> confirmed the favorable influence of radiotherapy. Sometimes the lesions recurred later, but resumption of treatment caused them to retrogress and disappear; this probably meant that the initial treatment had not been continued long enough. The evidence furnished by the group of writers last mentioned indicates that the action of the rays is greatest during the early stages of the granular form of the disease and least during the late stages, when the granulations have been replaced by connective tissue.

**Chronic Arthritis.**—In many cases roentgen irradiation relieves pain and reduces swelling, and the functional disability diminishes. As might be expected, the degree of improvement varies considerably with different patients. The best results require repeated treatment and are obtained in cases in which the inflammation is active. Incidentally, a useful indication of active inflammation is tenderness. When the inflammatory deposits have become largely or completely organized, little improvement is to be expected. Of course, focal infection and other abnormalities must not be neglected, irrespective of irradiation.

**Bronchiectasis.**—Recently Berck and Harris<sup>27</sup> reported having treated with roentgen rays thirty patients with bronchiectasis, of whom nineteen are said to have derived more or less pronounced improvement. Here again an opinion about the value of irradiation will have to await corroborative testimony. However, the care with which the cases appear to have been selected and the degree of improvement obtained in many of them make this report seem worthy of attention.

#### GENERAL

**Quality of Rays.**—The quality of the rays is of secondary importance. Favorable results can be obtained with rays generated at 100, 140 or 200 kilovolts. If in most cases the results obtained with rays generated at 130 or 140 kilovolts seem superior to those obtained with rays generated at a high potential, this is almost certainly not due to any specific action of rays of different wavelength but probably to a difference in absorption by the inflamed tissues. A larger proportion of rays of medium wavelength than of rays of short wavelength is absorbed in the first few centimeters of tissue. Therefore, since the majority of the inflammatory conditions mentioned are near the surface, the advantage, so far as maximal absorption at the desired level is concerned, would seem to favor rays of medium wavelength. When the inflammation is deep in the thorax, rays of short wavelength might be preferable. However, since the most effective dose is small, this theoretical advantage is not an important factor.

One consideration cannot be stressed too much, and the inability of some radiologists to obtain satisfac-

tory results is often due to their failure to realize its importance. This consideration is that, in chronic inflammations generally, treatment must be repeated at regular intervals for a variable period. Even after the lesions and symptoms have disappeared or have ceased to be active, it is wise to treat the patient once or twice more. The more chronic the lesion, the more essential is this precaution. As examples I need only cite tuberculous adenitis, peritonitis, arthritis and synovitis. The response of tuberculous lesions to roentgen irradiation varies considerably from one patient to another, but in general it is characteristically slow. When treatment is stopped too soon, what might have been an excellent and permanent result is spoiled; after a period of apparent arrest, the tuberculous process becomes active again and resumption of treatment may not be so effective as before. Greater persistence in the first instance is usually the best policy.

When dealing with acute or chronic inflammatory lesions, a most important point is that the concept of maximal, tolerance or tumor doses must be abandoned. Not only are they less effective, but they are actually dangerous. To employ such doses in treating inflammatory conditions constitutes a loss of electrical energy, a gross waste of time on the part of the personnel as well as that of the patient and an unwarranted increase in cost. But, still more important, there is danger of inducing in the affected tissues an inflammatory reaction independent of that which is already present, and this might readily lead to spread rather than resolution of the infection. The principles of sound treatment are thus violated. This probably explains why some radiologists have failed to obtain the favorable results which should follow proper treatment. Furthermore, the possibility of spreading the infection by excessive doses is not the only danger. Experiments on animals, carried out by Lacassagne and Vinzent,<sup>28</sup> have shown that, when acute inflammatory lesions induced by injecting *Streptobacillus caviae* into rabbits were exposed to doses of roentgen rays such as are used in the treatment of malignant processes, in a considerable proportion of animals sarcomas subsequently developed in the same region.

#### MODE OF ACTION

**Acute Inflammations.**—Numerous experiments have long since made it clear that most bacteria are not directly influenced to a perceptible degree by doses of roentgen rays or radium such as are commonly employed in treating human beings. To attribute the favorable effect of irradiation to a bactericidal action of the rays, therefore, would be to maintain an untenable hypothesis. Certainly there is little ground for the assumption that irradiation increases the production of antibodies. On the contrary, the experiments of Hektoen<sup>29</sup> and of others indicate that irradiation tends to diminish the formation of antibodies. Nor does the evidence now available justify one in assuming that

22. Stephenson, Sydney, and Walsh, David: Short Note on the Cure of Trachoma by X-Ray Tube Exposure and by High Frequency Brush Discharges, *Lancet* 1: 237 (Jan. 24) 1903.

23. Cassidy, H. F., and Rayne, F. C.: Trachome chronique très amélioré par les rayons X, *Tr. Ann. d'électrobiol.* 6: 617-619, 1903.

24. Thielemann, Rudolf: Zur Wirkungsweise des Radiumbestrahlung auf die trachomatöse Bindehaut, *Ztschr. f. Augenh.* 14: 559-569, 1905.

25. Cochard, M.: La radiothérapie du trachome, Thesis 128, Lyons, 1921.

26. Meldolesi, G., and Sabbadini, D.: Sulla terapia del tracoma con le razzioni secondarie ottenute col metodo del Ghilarducci, *Radiol. med.* 10: 222, 1923.

27. Berck, Maurice, and Harris, William: Roentgen Therapy in Bronchiectasis, *J. A. M. A.* 108: 517-522 (Feb. 13) 1937.

28. Lacassagne, A.: Tumeurs malignes provoquées, chez le lapin, par l'irradiation de foyers inflammatoires, *Compt. rend. Acad. d. sc.* 196: 69-71 (Jan. 3) 1933; Conditions dans lesquelles ont été obtenus, chez le lapin, des cancers par action des rayons X sur des foyers inflammatoires, *Compt. rend. Soc. de biol.* 112: 562-564 (Feb. 17) 1933; Cancers Produced in Rabbits by the Action of X-Rays on Inflammatory Lesions, *Brit. J. Radiol.* 6: 689-691 (Nov.) 1933. Lacassagne, A., and Vinzent, R.: Action des rayons X sur un foyer infectieux local, provoqué chez le lapin par l'injection de *Streptobacillus caviae*, *Compt. rend. Soc. de biol.* 100: 247-249 (Jan. 26) 1929; Sarcomes provoqués chez des lapins par l'irradiation d'abcès à *Streptobacillus caviae*, *ibid.* 100: 249-251 (Jan. 26) 1929.

29. Hektoen, Ludvig: The Influence of X-Rays on the Production of Antibodies, *J. Infect. Dis.* 17: 415-422 (Sept.) 1915; Further Studies on the Effects of the Roentgen Rays on Antibody Production, *ibid.* 22: 28-33 (Jan.) 1918; Further Observations on the Effects of Roentgenization and Splenectomy on Antibody Production, *ibid.* 27: 23-30 (July) 1920.



any difference in the quality of the rays has a direct effect on the result, but the quality of the rays may and probably does have an indirect effect because it influences the proportion of rays absorbed at different depths beneath the surface.

Any one who has had an extended experience with radiotherapy for acute inflammations cannot have failed to be impressed (1) by the prompt relief of pain and the rapid resolution of the lesions when treated early, as well as by the acceleration of suppuration in lesions treated later, (2) by the fact that acute inflammations of different kinds respond at about the same rate to a given dose when treated at a corresponding stage and (3) by the circumstance that a small dose of rays is sufficient to produce this effect. Since irradiation acts in the same way and in the same time on so many forms of acute inflammation, it seems logical to conclude that the lesions themselves must have some common factor. This factor appears to be the radio-sensitiveness of certain cells which are a more or less prominent feature of the majority of acute inflammations.

Pyogenic infections in general are characterized by varying degrees of leukocytic infiltration. By accumulating leukocytes, chiefly lymphocytes, polymorphonuclear cells and eosinophils, around one or more clusters of bacteria, the body attempts to localize the infection, to destroy the invading organisms and to neutralize their toxic products. The leukocytic infiltration also appears to be nature's method of intensifying the production of antibodies. An additional factor is hyperemia, which facilitates the mobilization of leukocytes. Of some acute inflammations, especially those caused by streptococcal infection, local infiltration by leukocytes is not a prominent feature. Against infections of this kind the body apparently defends itself by a general reaction of the leukocytes in the circulating blood.

Experiments on a large number of animals of different species and observations on human beings of the effect of roentgen rays and radium on different kinds of cells and tissues have proved conclusively that each variety of cell has a specific range of sensitiveness to irradiation. Some are extremely sensitive, even to small doses, while others are not influenced by doses many times larger. Moreover, these experimental and clinical investigations have demonstrated that the most sensitive of all cells are the lymphocytes in the spleen, lymph nodes, lymph follicles, thymus gland, circulating blood and bone marrow. The polymorphonuclear and eosinophilic leukocytes are also sensitive, but their susceptibility to irradiation is slightly less than that of the lymphocytes. When the entire body of an animal is exposed to a moderate dose of roentgen rays or radium, the majority of the organs remain free from perceptible abnormalities, but the spleen, lymph nodes and intestinal lymph follicles show a destruction of lymphocytes, the degree of which varies according to the dose of rays and the interval between irradiation and microscopic examination.

As observed by Heineke,<sup>30</sup> the disintegration of lymphocytes was characterized by disorganization and fragmentation of the nuclear chromatin of the cells and by scattering of the fragments of chromatin between

the remaining intact cells and in the spaces of the reticular stroma, where the fragments gathered into clumps or balls. Then the clumps or balls of degenerate chromatin were gradually taken up by some of the reticular cells, which assumed a phagocytic property and swelled as the amount of ingested chromatin debris increased. This was associated with a progressive reduction in volume of the affected lymphoid structures. Identical changes were observed in the lymphoid tissue of the vermiform appendix and in the bone marrow. The destruction of lymphocytes in the spleen and lymph nodes was often so great that most of the malpighian corpuscles or lymph follicles could be recognized only by the blood vessels and by the concentric arrangement of the stroma. A small percentage of lymphocytes appeared to resist the action of the rays. After a number of hours the phagocytic reticular cells (macrophages) themselves began to disappear. The chromatin debris ingested by the phagocytes appeared to undergo intracellular digestion because the number and size of the ingested fragments diminished steadily. Two or three days after irradiation, degenerative alteration of other cells, notably the polymorphonuclear leukocytes and eosinophils, also became perceptible, and many of these cells disappeared from the splenic pulp and bone marrow. From ten days to three weeks later, more or less regeneration of the lymphoid tissue became evident.

Since then, Heineke's results have been confirmed by many investigators, including Krause and Ziegler,<sup>31</sup> Fromme,<sup>32</sup> Hall and Whipple,<sup>33</sup> Warthin,<sup>34</sup> Tsuzuki,<sup>35</sup> and many others. Warthin's description of the effect of roentgen rays corroborated the observations of Heineke in every particular except that, by examining the tissue soon after irradiation, Warthin found unmistakable evidence of the disintegration of lymphocytes within fifteen minutes after exposure of the animals to the rays, and the cellular degeneration continued for several days. Similar effects have been obtained with radium. Other investigators have demonstrated that the lymphocytes in the circulating blood are equally sensitive to irradiation and that the circulating polymorphonuclear and eosinophilic leukocytes are only slightly less sensitive than the lymphocytes.

The rate at which the varieties of leukocytes mentioned are destroyed by irradiation under experimental conditions corresponds closely to the rate at which acute inflammations subside after exposure to a suitable dose of roentgen rays or radium. The only other cells in the body which are affected at anything like the same rate are the mucus-secreting epithelial cells in the salivary glands, in the bronchi and in the intestine; but since these cells could not play any part in the majority of inflammatory processes, they may be excluded from consideration.

In circumscribed inflammations the significant role of lymphocytes, polymorphonuclear cells and eosinophils in the defense of the organism against infection and the sensitiveness of these cells to irradiation make it appear likely that, when an inflammatory lesion is irradiated, the rays act mainly by destroying a proportion of the

30. Heineke, H.: Ueber die Einwirkung der Röntgenstrahlen auf Tiere. München. med. Wehnschr. 1: 2090-2092 (Dec.) 1903; Zur Kenntnis der Wirkung der Radiumstrahlen auf tierische Gewebe, *ibid.* 2: 1382-1384 (Aug. 2) 1904; Experimentelle Untersuchungen über die Einwirkung der Röntgenstrahlen auf innere Organe, *Mitt. u. d. Grenzgeb. d. Med. u. Chir.* 14: 21-94, 1905.

31. Krause, Paul, and Ziegler, Kurt: Experimentelle Untersuchungen über die Einwirkung der Röntgenstrahlen auf tierisches Gewebe, *Fortschr. a. d. Geb. d. Röntgenstrahlen*. 10: 126-182, 1906.

32. Fromme, G.: Ueber die allgemeine Wirkung der Röntgen- und Radiumstrahlen, *Ztschr. f. Geburtsh. u. Gynäk.* 70: 579-613, 1917.

33. Hall, C. C., and Whipple, G. H.: Roentgen Ray Intoxication: Disturbances in Metabolism Produced by Deep Massive Doses of the Hard Roentgen Rays, *Am. J. M. Sc.* 157: 453-482 (April) 1919.

34. Warthin, A. S.: An Experimental Study of the Effect of Roentgen Rays on the Blood-Forming Organs, with Special Reference to the Treatment of Leukemia, *Internat. Clin.* 4: 243-277, 1906.

35. Tsuzuki, Masao: Experimental Studies on the Biological Action of Hard Roentgen Rays, *Am. J. Roentgenol.* 16: 134-150 (Aug.) 1926.

leukocytes infiltrating the lesion or circulating in the blood vessels which supply the affected region. This view is corroborated by the rapidity with which the symptoms often abate and the physical signs disappear. Moreover, microscopic examination of irradiated inflammatory lesions has repeatedly shown destruction of leukocytes, especially lymphocytes, to be the outstanding feature observed. It seems logical to conclude, therefore, that destruction of leukocytes is the primary and direct effect of irradiation. As a result of the disintegration of infiltrating leukocytes the antibodies, ferments and other protective substances which these cells contained are liberated in the surrounding tissue spaces, where they become mixed with the tissue fluids. It is also probable, as the experimental evidence indicates, that the next step is an increase in phagocytosis by reticular cells which become macrophages. No doubt other intimate, secondary or indirect effects related to cell metabolism are produced, but the precise character and significance of these effects are not clear.

Since leukocytic infiltration is an outstanding factor in the defense against infection, the natural question is why destruction of a large number of leukocytes infiltrating such lesions may not do more harm than good. The only answer is that, after small or moderate doses, no one has yet submitted any evidence of ill effects. The influence of irradiation always has been favorable or the rays have failed to alter the course of the inflammatory process.

From the foregoing considerations, therefore, it seems not unreasonable to assume that irradiation, by destroying some of the infiltrating leukocytes, causes the protective substances in these cells to be liberated and to be made even more readily available for defensive purposes than when they were in the intact cells. This and the increase in phagocytosis which follows the disintegration of the cells represent the main effects of exposure to roentgen rays and radium and probably explain the usually favorable action to these agents.

All the clinical circumstances indicate that inflammatory lesions respond to irradiation in proportion to the degree of leukocytic infiltration. In favor of this view are the experimentally proved radiosensitiveness of lymphocytes, polymorphonuclear leukocytes and eosinophils, the fact that the rate of regression of acute inflammations corresponds to the rate at which these cells are known to be destroyed by irradiation, and that these cells are the only cells commonly found in inflammatory lesions that could be affected at such a rapid rate by small or moderate doses. Other circumstances pointing in the same direction are that radiotherapy is most beneficial during the suppurative stage and less beneficial during the suppurative stage and that, although the majority of lesions yield rapidly to treatment, some respond less rapidly or do not respond at all. Variation in the degree of leukocytic infiltration of different lesions of the same character or of similar lesions of different character is a well known pathologic fact. Therefore the degree of leukocytic infiltration must influence the action of the rays, because the rays can destroy leukocytes only in proportion to the number of these cells. This is undoubtedly related to and probably explains the fact that, while many inflammatory lesions are influenced favorably, some react much less or do not show any reaction.

When the inflammation is not confined to a small region but is extensive or diffuse rather than circumscribed, and when leukocytic infiltration is not a pronounced feature, as in erysipelas, the rays probably act

in a somewhat different manner. Under these circumstances the smaller number of infiltrating leukocytes should prevent the rays from having the same local effect unless some compensatory mechanism enters into play. Evidence of such a mechanism in erysipelas has not yet been demonstrated, but that such a mechanism exists is indicated by the action of roentgen rays in other diseases. In bronchial asthma, for example, irradiation of the spleen or of other parts of the body remote from the bronchi and lungs is often followed by more or less striking relief from symptoms. What probably takes place is a destruction of leukocytes in the spleen and in the large mass of blood circulating through this organ. Then the cellular debris and the contents of the destroyed cells find their way into the general circulation, where they have been shown to produce a protein-like reaction. In inflammations that are not circumscribed and in which leukocytic infiltration is comparatively slight, the affected region is hyperemic and the vessels are more or less gorged with blood. Wide exposure of such a region to a small dose of rays undoubtedly causes many leukocytes to disintegrate, and the contents of the destroyed cells are liberated into the blood and throughout the tissue spaces. And the destruction of leukocytes is probably followed by changes similar to those described in connection with more limited inflammations. At least this would seem to be the most logical conclusion. Any other assumption would be inconsistent with the known facts and with the clinical behavior of this kind of inflammation.

*Chronic Inflammations.*—To understand the influence of irradiation on chronic inflammations it is necessary to bear in mind a few essential points. Depending on their character and on the etiologic factors which produce them, such lesions are characterized by varying degrees of leukocytic infiltration, connective tissue proliferation and caseous, calcareous or hyaline degeneration. Moreover, the clinical effect of irradiation is slow, and maximal improvement or cure requires repeated treatment at intervals. From what is known about the action of roentgen rays and radium on different varieties of cells and tissues, it seems most likely that these factors are closely related. Since they are products of cellular degeneration, caseous material and calcium deposited as the final stage of healing should not be influenced by irradiation, and this is precisely what is observed in practice. As we have already seen, the varieties of leukocytes which are such an important feature of inflammatory infiltration are exceptionally sensitive to roentgen rays or radium. Connective tissue cells, on the contrary, are comparatively resistant to irradiation; they are even less sensitive than the epithelium of the skin. In this respect the difference between lymphocytes or polymorphonuclear leukocytes and connective tissue cells is tremendous.

Analysis and correlation of these several factors would seem to furnish a satisfactory explanation of the effect of radiotherapy on chronic inflammatory processes. The greater the degree of leukocytic infiltration in proportion to connective tissue proliferation, the more marked and the more rapid is the influence of the treatment, and vice versa. If tuberculous lesions are taken as an example, it is well known that the effect of irradiation is greater during the infiltrative phase of the tubercles, when leukocytic infiltration is most pronounced, than it is when the leukocytic infiltration has diminished and has passed into an advanced stage of caseous degeneration or of repair by connective tissue or by calcification.

It is probable, therefore, that leukocytic infiltration, on the one hand, and connective tissue proliferation, on the other, act in opposite directions, the former tending to increase the effect of irradiation and the latter tending to diminish or retard this effect. This conclusion is in complete harmony with the experimental evidence and with all the clinical observations which have been recorded.

## Council on Foods and Nutrition

### ACCEPTED FOODS

THE FOLLOWING ADDITIONAL FOODS HAVE BEEN ACCEPTED AS CONFORMING TO THE RULES OF THE COUNCIL ON FOODS AND NUTRITION OF THE AMERICAN MEDICAL ASSOCIATION FOR ADMISSION TO ACCEPTED FOODS.

FRANKLIN C. BING, Secretary.

### FATS AND OILS AND THEIR PRODUCTS (See Accepted Foods, 1939, p. 30).

Interstate Cotton Oil Refining Co., Sherman, Texas.

Mrs. TUCKER'S SALAD OIL, refined cottonseed oil with a small amount (24 parts per million) of lecithin.

*Analysis* (submitted by manufacturer).—Specific gravity at 25 C. 0.9095, saponification value 190.8, iodine number 104.8, free fatty acids as oleic acid 0.03%, cold test (hours remaining brilliant at 0 C.) 8½ hours.

*Calories*.—9 per gram; 256 per ounce.

### FOODS, FOR SPECIAL DIETETIC PURPOSES (See Accepted Foods, 1939, p. 295).

The Chicago Dietetic Supply House, Inc.

CELLU BRAND JUICE-PAK HAWAIIAN PINEAPPLE TIDBITS, without added sugar.

*Analysis* (submitted by manufacturer).—Moisture 83.7%, total solids 16.3%, ash 0.4%, fat (ether extract) trace, protein (N  $\times$  6.25) 0.4%, crude fiber 0.3%, carbohydrates other than crude fiber 15.2%.

*Calories*.—0.62 per gram; 18 per ounce.

CELLU BRAND JUICE-PAK SLICED YELLOW CLING PEACHES, without added sugar.

*Analysis* (submitted by manufacturer).—Moisture 90.1%, total solids 9.9%, ash 0.4%, fat (ether extract) 0.2%, protein (N  $\times$  6.25) 0.3%, crude fiber 0.3%, carbohydrates other than crude fiber (by difference) 8.7%.

*Calories*.—0.38 per gram; 11 per ounce.

### FRUIT JUICES INCLUDING TOMATO JUICE (See Accepted Foods, 1939, p. 48).

Ladoga Canning Company, Indianapolis.

SUGAR LOAF BRAND TOMATO JUICE.

*Analysis* (submitted by manufacturer).—Moisture 94.0%, total solids 6.0%, ash 0.84%, sodium chloride (NaCl) 0.7%, water insoluble solids 0.4%, invert sugar 2.8%, carbohydrates (by difference) 4.5%, acidity 0.4%, acidity expressed as pH 4.33.

The firm reports that chemical titration (1937) showed that the canned tomato juice contained 17.2 mg. of ascorbic acid (344 international units of vitamin C) per 100 cc. Samples of raw tomatoes used in making the juice were found to contain 22.7 mg. (454 international units) of vitamin C per 100 cc.

*Calories*.—0.18 per gram; 5 per ounce.

The C. H. Musselman Company, Elgerville, Pa.

MUSSELMAN'S BRAND TOMATO JUICE.

*Analysis* (submitted by manufacturer).—Moisture 93.4%, total solids 6.6%, ash 1.0%, fat 0.1%, protein (N  $\times$  6.25) 1.0%, crude fiber 0.2%, carbohydrate other than crude fiber (by difference) 4.3%, reducing sugar as invert 3.2%.

The firm reports (1940) that chemical titration showed that the canned tomato juice contains from 18 to 23 mg. of ascorbic acid (from 372 to 454 international units of vitamin C) per 100 cc.

*Calories*.—0.20 per gram; 6 per ounce.

### GRAIN PRODUCTS (See Accepted Foods, 1939, p. 95).

The Kansas Milling Company, Wichita, Kan.

SILK FLOSS BRAND CAKE FLOUR, white flour milled from soft winter wheat, bleached, heat treated.

*Analysis* (submitted by manufacturer).—Moisture 12.5%, total solids 87.5%, ash 0.3%, fat (ether extract) 1.0%, protein (N  $\times$  5.7) 8.0%, crude fiber 0.2%, carbohydrates other than crude fiber (by difference) 78.0%.

*Calories*.—3.5 per gram; 99 per ounce.

### MILK AND MILK PRODUCTS OTHER THAN BUTTER (See Accepted Foods, 1939, p. 230).

Newaygo Creamery Company, Newaygo, Mich.

SPARTAN BRAND EVAPORATED MILK.

*Analysis* (submitted by manufacturer).—Moisture 74%, total solids 26%, ash 1.5%, fat (Roesse-Gottlieb method) 7.9%, protein (N  $\times$  6.38) 7%, carbohydrates (by difference) 9.6%.

*Calories*.—1.38 per gram; 39 per ounce.

### PREPARATIONS USED IN THE FEEDING OF INFANTS (See Accepted Foods, 1939, p. 156).

H. J. Heinz Company, Pittsburgh.

HEINZ BRAND CHOPPED MIXED VEGETABLES, a canned, cooked chopped mixture of white potatoes, carrots, sweet potatoes, celery, green beans, onions and sodium chloride.

*Analysis* (submitted by manufacturer).—Moisture 89.8%, total solids, 10.2%, ash 1.1%, fat (ether extract) 0.1%, protein (N  $\times$  6.25) 0.8%, crude fiber 0.5%, carbohydrates other than crude fiber (by difference) 7.7%, sucrose (Munson and Walker method) 2.7%, calcium (Ca) 0.030%, phosphorus (P) 0.026%, iron (Fe) 0.0054%, copper (Cu) 0.00004%.

According to report of biologic assay (1939) this product contains 1,700 international units of vitamin A, 9 international units of vitamin B<sub>1</sub> and 22 Sherman-Bourquin units of riboflavin per hundred grams. Report of chemical titration (1939) shows that the product contains 36 international units of vitamin C per hundred grams.

*Calories*.—0.35 per gram; 10 per ounce.

HEINZ BRAND CHOPPED SPINACH.

*Analysis* (submitted by manufacturer).—Moisture 94.5%, total solids 5.5%, ash 1.1%, fat (ether extract) 0.2%, protein (N  $\times$  6.25) 1.8%, crude fiber 0.7%, carbohydrates other than crude fiber (by difference) 1.7%, sucrose (Munson and Walker method) 0.4%, calcium (Ca) 0.174%, phosphorus (P) 0.035%, iron (Fe) 0.0023%, copper (Cu) 0.00008%.

According to report of biologic assay (1939) this product contains 4,500 international units of vitamin A, 11 international units of vitamin B<sub>1</sub> and 78 Sherman-Bourquin units of riboflavin per hundred grams. Report of chemical titration (1939) shows that the product contains 200 international units of vitamin C per hundred grams.

*Calories*.—0.16 per gram; 5 per ounce.

HEINZ BRAND CREAMED DICED POTATOES WITH ONIONS AND YEAST CONCENTRATE, a canned cooked mixture of white potatoes, milk, onions, cream (40% butterfat), flour, butter, sodium chloride and dried brewers' yeast.

*Analysis* (submitted by manufacturer).—Moisture 84.9%, total solids 15.1%, ash 1.3%, fat (ether extract) 2.5%, protein (N  $\times$  6.25) 1.7%, crude fiber 0.6%, carbohydrates other than crude fiber (by difference) 9.0%, sucrose (Munson and Walker method) 1.0%, calcium (Ca) 0.027%, phosphorus (P) 0.086%, iron (Fe) 0.00056%, copper (Cu) 0.00013%.

According to report of biologic assay (1939) this product contains 110 international units of vitamin A, 11 international units of vitamin B<sub>1</sub> and 37 Sherman-Bourquin units of riboflavin per hundred grams. Report of chemical titration (1939) shows that the product contains 62 international units of vitamin C per hundred grams.

*Calories*.—0.65 per gram; 18 per ounce.

HEINZ BRAND CREAMED GREEN VEGETABLES, a canned cooked mixture of milk, finely chopped green lettuce, peas, kale and asparagus, cream, flour and sodium chloride.

*Analysis* (submitted by manufacturer).—Moisture 87.2%, total solids 12.8%, ash 1.4%, fat (ether extract) 2.6%, protein (N  $\times$  6.25) 2.6%, crude fiber 0.9%, total carbohydrates other than crude fiber (by difference) 5.3%, sucrose (Munson and Walker Method) 2.1%, calcium (Ca) 0.060%, phosphorus (P) 0.050%, iron (Fe) 0.0046%, copper (Cu) 0.00023%.

According to report of biologic assay (1939) this product contains 845 international units of vitamin A, 17 international units of vitamin B<sub>1</sub> and 58 Sherman-Bourquin units of riboflavin per hundred grams. Report of chemical titration (1939) shows that the product contains 64 international units of vitamin C per hundred grams.

*Calories*.—0.55 per gram; 16 per ounce.

HEINZ BRAND CREAMED TOMATO AND RICE WITH VEGETABLES AND WHEY POWDER, a canned cooked mixture of tomatoes, carrots, white potatoes, cream, celery, sugar, rice, milk, whey powder, soya bean flour and sodium chloride.

*Analysis* (submitted by manufacturer).—Moisture 82.0%, total solids 18.0%, ash 1.7%, fat (ether extract) 2.2%, protein (N  $\times$  6.25) 2.1%, crude fiber 0.6%, carbohydrates other than crude fiber (by difference) 11.4%, sucrose (Munson and Walker Method) 7.2%, calcium (Ca) 0.032%, phosphorus (P) 0.044%, iron (Fe) 0.0017%, copper (Cu) 0.00066%.

According to report of biologic assay (1939) this product contains 1,480 international units of vitamin A, 20 international units of vitamin B<sub>1</sub> and 39 Sherman-Bourquin units of riboflavin per hundred grams. Report of chemical titration (1939) shows that the product contains 200 international units of vitamin C per hundred grams.

*Calories*.—0.74 per gram; 21 per ounce.

### SUGARS AND SYRUPS (See Accepted Foods, 1939, p. 324).

Bliss Syrup & Preserving Co., Kansas City, Mo.

NECTAR BRAND CRYSTAL WHITE SYRUP, a mixture of corn syrup, cane sugar syrup, flavored with vanilla and a small amount of sodium chloride.

*Analysis* (submitted by manufacturer).—Moisture 24.5%, total solids 75.5%, ash 0.2%, reducing sugars as dextrose 30.0%, reducing sugars as dextrose after inversion with invertase 35.0%, sucrose (copper reduction method) 4.9%, dextrins (by difference) 40.4%.

*Calories*.—3.01 per gram; 85 per ounce.

Wood's Mince Meat Company, Baltimore.

WOOD'S GOLDEN SYRUP, a mixture of corn syrup, refiners' syrup and sugar syrup.

*Analysis* (submitted by manufacturer).—Moisture 20.8%, total solids 79.2%, ash 0.7%, protein (N  $\times$  6.25) 0.06%, reducing sugars as dextrose after inversion 38.2%, sucrose 2.4%, dextrins (by difference) 37.8%, specific gravity at 20 C. 1.4, specific gravity at 60 F. 40.4 degrees Baume.

*Calories*.—3.2 per gram; 91 per ounce.

# THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

535 NORTH DEARBORN STREET - - - CHICAGO, ILL.

Cable Address - - - "Medic, Chicago"

Subscription price - - - Eight dollars per annum in advance

*Please send in promptly notice of change of address, giving both old and new; always state whether the change is temporary or permanent. Such notice should mention all journals received from this office. Important information regarding contributions will be found on second advertising page following reading matter.*

SATURDAY, JANUARY 18, 1941

## "VITAMIN SWEETS"

On January 9 the publicity agency for the British American Ambulance Corps released a mimeographed news statement to the American press stating that tablets to be known as "Vitamin Sweets" were being prepared in great quantities for shipment to England. According to information just obtained, the tablets of "Vitamin Sweets" were to contain vitamin A 7,000 international units,<sup>1</sup> vitamin B<sub>1</sub> 700 international units, riboflavin 4.6 mg., ascorbic acid 70 mg., vitamin D 700 international units, and sucrose with flavoring 21 Gm., this amount to make one roll of fourteen tablets. The children of Great Britain, it was suggested, would receive six tablets daily. According to the newspaper release, these are all the vitamins necessary to prevent deficiency disease. It was stated that "an adequate supply of these vitamins will prevent such symptoms as moodiness, sluggishness, fear, mental and physical fatigue as well as the ordinary deficiency diseases such as rickets, scurvy, beriberi, pellagra, cheilosis (sores around the mouth) and 'blackout blindness.'" Such claims are of course preposterous and far exceed those permitted by any recognized group having to do with vitamins, including the Council on Pharmacy and Chemistry and the Council on Foods and Nutrition. Such publicity undoes much of the work of the Food and Drug Administration and of the Federal Trade Commission, which have been trying to keep claims for commercial vitamin preparations within reason. "For \$8.55, 156 rolls of 'Vitamin Sweets' sufficient for one child for a year may be purchased in this country for shipment to Britain," according to a representative of the British American Ambulance Corps. Apparently some sincere, well intentioned physicians approached the British Ministry of Health about the possibility that American friends of the British could supply sugar tablets containing vitamins. Sugar was rationed, the British people liked sugar, and vitamins,

1. The vitamin A is probably an ester from fish liver oil concentrate. The Eastman Kodak Company has been working on such a preparation.

it was thought, would be more acceptable in this form. The Ministry of Health stated it was grateful for the offer. In the meantime, six American authorities in the field of nutrition consented to serve on the committee and to consider the plan; hence the publicity referring to the panel of six well known physicians who had collaborated in devising a new formula with the advice and cooperation of the British minister of health. Unfortunately, according to available information, most of these physicians had not endorsed or been informed of the contents of the publicity sent out by the agency of the British American Ambulance Corps.

In the release it was stated that "a committee called 'Vitamins for Britain' obtained the services of Dr. Philip Newton, an expert in the pharmacologic blending of several vitamins, who worked out for us a method by which vitamins A, B<sub>1</sub>, B<sub>2</sub>, C and D could all be incorporated in a flavored candy stick." Concerning the identity of Dr. Newton, a telegraphic inquiry was sent to the British American Ambulance Corps. The reply verified that he is apparently the same Philip Newton who was described in *THE JOURNAL* Nov. 12, 1927 as the promoter of Matamel, a nostrum which had been puffed as a cure for Bright's disease, bladder trouble and hypertrophy of the prostate. In 1926 he signed an agreement with the Post Office authorities, stipulating that the mail order business operated by the Newton Laboratories would be discontinued and abandoned. Previously, the New York papers in August 1924 had reported that Newton had been arraigned in the court of the city of New York on charges of violating a penal law which prohibits placing in newspapers advertisements relating to certain diseases.

The Council on Foods and Nutrition has not adopted the proposal that vitamins be incorporated in "sweets" as far as the American market is concerned. The plan proposed cannot be considered other than an experiment. The unwise propaganda might well lead to commercialism in this country of synthetic vitamins in so-called vitamin candy. Sufficient evidence of what might be the effect of vitamin D in diets low in calcium and phosphorus is not available. Likely the children may suffer from lack of food in general. The vitamin mixture is certainly not complete; it does not provide all the vitamins necessary to prevent deficiency diseases. As far as *THE JOURNAL* is aware there is no practical evidence of the stability of these tablets. There should be no implications that, by supplying vitamins alone, health may be maintained.

In times of war, hysterical overenthusiasm should not influence the scientific thought of authorities. Publicity arising in this country dealing with problems of health in belligerent countries must consider the effect of such publicity on American citizens in the light of American ideals and standards.

## UNIONIZATION OF HOSPITAL EMPLOYEES

Efforts on the part of unions in Pennsylvania to unionize hospital employees were recently surveyed critically in connection with a case decided by the Supreme Court of Pennsylvania on January 6.<sup>1</sup> Apparently, attempts to form a union among hospital employees were opposed by the officials of some twenty-five hospitals involved. The hospitals refused to execute a proposed agreement with the unions or to negotiate any agreement, and the unions then appealed to the Pennsylvania Labor Relations Board, charging unfair labor practices on the part of the hospitals. The matter came before the court of common pleas of Dauphin County when the hospitals filed a bill for an injunction to restrain the Labor Relations Board and the unions from proceeding with the plans under consideration. This petition stated that the formation of a union among hospital employees would result in demands of such a character as to jeopardize the financial ability of the hospitals to function and that efforts to enforce these demands by strikes or otherwise would seriously imperil the management of the hospitals and the lives, health and safety of the patients. It was pointed out that the demands already made would entail an increased yearly outlay of more than \$2,000,000 and would, if granted, in effect transfer control of the hospitals from their officials to the unions. The lower court granted the preliminary injunction, giving the relief sought, and the defendants appealed to the Supreme Court of Pennsylvania, which in a per curiam decision affirmed the decree of the court below.

The first question disposed of in this case was whether the State Labor Anti-Injunction Act prevented the court from issuing the injunction sought by the hospitals. That act applies to situations involving or growing out of "a labor dispute when the case involves persons who are engaged in a single industry, trade, craft, or occupation." In holding that this act had no application to the facts involved in the case before it, the court asserted that a hospital is not an industry nor are the employees of a hospital engaged in a single trade, craft or occupation. Student nurses, the court pointed out, interns, doctors, surgeons, clerks, stenographers, bookkeepers, elevator operators, ambulance drivers, laundresses, mechanics, technicians, charwomen and others may be employed by a hospital and they may have a common employer but they have no single trade, craft or occupation. Giving the words "industry, trade, craft, or occupation" their commonly accepted meaning, the court did not feel that they include the operations of a hospital. "Even though the words of the statute be interpreted as broad enough to include the operations of a hospital," the court continued, "we

do not think that the legislature intended such a result. The purpose of the Act is to preserve the status quo during labor disputes, to insure the right to bargain collectively, and to give to employees the right to choose representatives for this purpose. To show the scope of the Act, the Legislature attempted to define cases which 'involve or grow out of a labor dispute.' In doing so, it used the words 'industry, trade, craft or occupation.' It has not been the custom in the past to unionize hospitals. The effect of unionization and attendant efforts to enforce demands would involve results far more sweeping and drastic than mere property rights. The question of profit for the employer or wages for the employee are not alone involved. It is not merely a matter of suspending operations, ceasing work and stopping production, such as might be true in a steel mill or automobile factory. It is a question of protecting the health, safety and, in many cases, the very lives of those persons who need the service a hospital is organized to render. The results are quite different and more extensive than are involved in an ordinary labor dispute. We cannot conceive that the Legislature intended to include hospitals within the purview of the Act. Consequently, even though the words used might conceivably be broad enough to include a hospital, nevertheless, a hospital is not within the spirit of the Act, and not being within the spirit, the Act does not apply to it."

Another question before the court was whether the Pennsylvania Labor Relations Act, designed to protect the right of employees to organize and bargain collectively, had any application. "Hospitals are scientific institutions," the court said, "created for a humane purpose in amelioration of the sufferings of mankind. They require for their successful operation highly skilled physicians, surgeons, technicians, experts and nurses. They likewise require the services of other persons, some of whom may be skilled and some unskilled. But the whole must be coordinated, controlled and uninterrupted to accomplish the general purpose. This would be impossible, should we hold the Labor Act applicable with all its attending ramifications, interruptions and possible cessation of service due to labor disputes and attending financial inability to function. Surely the Legislature had no such intention and we cannot so find in the absence of a clear and positive declaration to that effect."

In addition, the court pointed to the fact that the term "employer" as defined by the Labor Relations Act excludes the commonwealth or any political subdivision thereof. While the hospitals involved in this case are not political subdivisions, the court said, they are, with few exceptions, agencies selected by the commonwealth as a means of assisting in some degree the indigent sick, disabled, injured or afflicted. "Should the state choose to operate general hospitals," the court pointed out, "as it does certain mental hospitals, no

1. *The Western Pennsylvania Hospitals, et al. v. Levi G. Lichtner, Harry Gifford, and William L. Dickel, constituting the Pennsylvania Labor Relations Board, et al., and Hospital Workers Local Union No. 255 of the State, County and Municipal Workers of America, Affiliated with the Congress of Industrial Organizations, et al.*

one would claim that it was not performing a function of government and in so doing is not an employer within the meaning of the Act. Since the State chooses to perform this function through agencies, supported in part by State appropriations, these agencies are likewise beyond the scope of the Act. Were this not so, the appropriations might be diverted from their intended purpose to aid the indigent sick, and injured to the payment of wages and increased operating costs." To the court it was obvious and indisputable that the hospitals involved in the case were impressed with a public interest which removed them from the purview of the Labor Relations Act. The opinion of Judge Richards in this case, which the Supreme Court characterized as "comprehensive," constitutes an important contribution to judicial literature and evidences a thorough understanding of the extremely important part played by hospitals in preserving the "health, safety and, in many cases, the very lives" of the people.

#### CALIFORNIA GOVERNOR ADVOCATES UNIVERSAL COMPULSORY HEALTH INSURANCE

Governor Olson of California in his message to the California legislature on January 6 made a specific recommendation that "California adopt a system of universal compulsory health insurance." The governor said:

The need and demand for such insurance is amply demonstrated by the many plans proposed or already in operation, including that advanced by the medical association. These plans are all constructive in purpose and many of them are quite useful within their limits but, by their very nature, they cannot meet the broad needs of society.

There is but one method that is socially adequate. That is the method already applied to workmen's compensation insurance, old age insurance and unemployment insurance. It is the method applied to health insurance in twenty-four of the twenty-seven countries having health insurance; that is, by making it both universal and compulsory. In our Department of Employment, which administers unemployment insurance in California, we already have the machinery and the organization to take over the work of administering a health insurance plan.

One can only conjecture as to the type of health insurance the governor would foist on the state. From the generality of the language in the meager reference, Governor Olson seems to be recommending something far beyond anything that the most vociferous health insurance fanatics have advocated. Even the so-called Epstein bill, drafted in 1934 for the American Association for Social Security and introduced in many state legislatures annually since that date, has not proposed universal coverage but provides exemptions with respect to income and employments. Governor Olson would apparently administer the nebulous scheme he proposes through a state department of employment. From such an administrative agency one could hardly anticipate any understanding of the medical needs of the population, any appreciation of available medical facilities or any intelligible comprehension of the innumerable problems that are essentially medical.

A proposal as far reaching as that of Governor Olson should be based on careful and adequate study of the factors involved; this proposal has not been based on any such study. True the California Medical Association conducted in the early thirties a statewide study of the medical needs and facilities of the state and expended well over \$50,000 of its own funds on the project. The state medical association cooperated with a state senate interim committee in a survey of the situation. After the house of delegates of the state association in a special session held late in 1934 by a close vote apparently endorsed the principle of compulsory health insurance, the interim committee and representatives of the state association jointly drafted a health insurance bill, which was introduced in the legislature in 1935. The measure was favorably reported out of committee but made no further legislative progress. That measure, however, is distantly, if at all, related to the system suggested by Governor Olson.

The California Medical Association has continued its efforts to procure an adequate solution to the medical problems of the lower and middle income group of the state. Quite properly it has felt its way slowly. After thoughtful evaluation of the situation a prepayment medical service plan limited somewhat as to services and available to the lower and middle income group has been put in operation. As experience and sound actuarial practices indicate and permit, it is proposed to widen the scope and availability of the plan. What the state association has done, it is believed, is sound and workable. If given the chance, the association's plan should fulfil the needs both of the public and of the medical profession. All of this obviously would be for naught and would be scrapped were any such actuarially unsound and socially undesirable measures as that urged by the governor to eventuate into law.

#### Current Comment

##### A DEFICIENCY DISEASE IN FOXES

A disease common on fox ranches called "Chastek paralysis" is a well defined syndrome characterized by a preliminary period of anorexia followed by the rapid development of weakness, ataxia and spastic paralysis. The outbreaks of this disease have for the most part occurred between November and May and invariably are on fox ranches where fish or fish products are fed as 10 per cent or more of the diet. This disease attains importance for man in its close clinical and pathologic resemblance to Wernicke's polioencephalitis. This type of polioencephalitis has been shown by Alexander to be due to a deficiency of vitamin B<sub>1</sub> in the presence of an adequate supply of other vitamins. The observations of Green and Evans<sup>1</sup> on Chastek paralysis make it clear that the disease in foxes is brought about by their eating fish and that the consumption of fish somehow

1. Green, R. G., and Evans, C. A.: A Deficiency Disease of Foxes. *Science* 92: 154 (Aug. 16) 1940.



produces a  $B_1$  avitaminosis in these animals. The mechanism by which it is brought about is not known. It has been suggested that some substance or substances in whole fresh fish and in alcoholic liquors are specifically destructive to vitamin  $B_1$  in these similar conditions in the fox and in man.

### INTERNS, RESIDENTS AND THE RESERVE CORPS

On December 19 the Adjutant General of the United States Army issued to all corps area and department commanders the following instructions:

1. The Surgeon General and Corps Area and Department Commanders are authorized to recommend for appointment sufficient applicants to fill any vacancies existing or occurring under the approved peacetime procurement objective for Reserve Officers in the Medical Department Reserve.

2. All appointments under this authority will be made in the lowest grade in the section in which commission is sought, and appointments will be limited to those who meet the requirements of AR 140-5 and AR 140-33.

3. Each application must be accompanied by a written statement by the applicant that he does not come within the category of those entitled to resign under the provisions of section 3 (c), Public Resolution 96, 76th Congress, or that he will not exercise such rights if ordered to active duty.

4. Current War Department instructions governing appointments in "affiliated" medical units continue unchanged.

The intent of these instructions is to enable the Surgeon General of the Army to commission in the Medical Reserve Corps young men who now hold positions as interns or residents or, indeed, any other medical positions of importance, and then to determine by suitable study whether or not their call to active service may be deferred until the completion of their internship or residency, or until their service is needed. The significant instruction is that under which the applicant agrees that he will not come within the category of those entitled to resign, and that he will not exercise the right to resign if ordered to active duty.

### THE HUMAN MECHANISM AND THE SUBMARINE

Because the submarine, especially under conditions of warfare, imposes certain environmental conditions not inherent on surface ships, medical problems of a particularly difficult nature develop in the care of the personnel. Recently Brown<sup>1</sup> has reviewed some of the problems faced by the medical officers responsible for the care of men on this exacting duty. First the selection of men must be especially rigid and the criteria must include strong eyes, keen hearing and the ability to equalize air pressure of 50 pounds to the square inch on the ear drum, since this quality is essential in escape training with the submarine "lung." Nervous stability is important, as a special nervous strain results from this type of work. Much study has been devoted to the vitiation of air which follows from respiration during submergence. The upper permissible limit for carbon dioxide is 3 per cent and the lower limit for oxygen 17 per cent, both of these including a margin of safety. Lethal or toxic gases have caused serious accidents: If sea water gains access to the storage batteries, sodium

chloride will be electrolyzed and chlorine evolved in dangerous volume. Another highly toxic gas which has led to poisoning is arsine, or arseniuretted hydrogen. Methyl chloride has also been known to produce dangerous poisoning in submarines. Besides gases, high temperatures and high humidities, especially under certain circumstances, produce serious problems during submerged operation. Numerous safety devices have been developed to counteract such hazards, including an analyzer to determine the concentration of carbon dioxide in the air and most notably the escape appliance better known as the submarine "lung" and designed for individual escape from the submarine. Finally, the special strain which submarine duty imposes on the personnel requires suitable facilities at the home base for comfort, relaxation and frequent leave periods.

### IMMUNIZATION AGAINST INFECTIOUS DISEASES IN THE ARMY

Efficiency among troops is dependent on good health. Among important health measures, as pointed out by Simmons,<sup>1</sup> are those prophylactic immunizations which can be carried out for infectious diseases. Three of them are applicable to all military personnel: smallpox, typhoid and paratyphoid, and tetanus. The effectiveness of vaccination against smallpox is so generally accepted as to make discussion unnecessary. Antityphoid vaccination has also been shown to be effective both for military personnel in time of war and for civil populations. However, the triple typhoid vaccine was discontinued after the last war and replaced first by the typhoid-paratyphoid A vaccine and later by a monovalent vaccine. Because of the present emergency and possible exposure to paratyphoid fevers, a triple typhoid vaccine has been readopted. The use of tetanus toxoid as a prophylactic has developed since the last war; it is now employed by practically all armies and has proved its usefulness. The initial vaccination with the toxoid as adopted by the army will consist of three 1 cc. doses given three weeks apart. This will be followed by subsequent doses of 1 cc. each given at the end of one year, at the time of departure for a theater of operations, if this occurs more than six months after the last dose received, or whenever the individual is wounded or otherwise exposed to infection with tetanus. In addition to these prophylactic agents there are methods of immunization available against localized outbreaks of disease endemic in this country such as diphtheria or scarlet fever. Some of the more serious diseases to which men in the continental United States would not ordinarily be exposed are subject to prophylactic inoculations of various degrees of established value including yellow fever, cholera, plague and typhus. Prophylactic inoculations against such infections as gas gangrene, malaria, relapsing fever, Oroya fever, the venereal infections, measles, mumps, meningitis, poliomyelitis and encephalitis constitute a further challenge. Experiments of an encouraging nature using pneumococcus polysaccharide solution for immunization against pneumonia have already taken place.

1. Brown, Capt. E. W.: The Human Mechanism and the Submarine, U. S. Naval Institute Proceedings 66:1608 (Nov.) 1940.

1. Simmons, J. S.: Immunization Against Infectious Diseases in the United States Army, South. M. J. 34:62 (Jan.) 1941.

## MEDICAL PREPAREDNESS

*In this section of The Journal each week will appear official notices by the Committee on Medical Preparedness of the American Medical Association, announcements by the Surgeon Generals of the Army, Navy and Public Health Service, and other governmental agencies dealing with medical preparedness, and such other information and announcements as will be useful to the medical profession.*

### CALL FOR ARMY NURSES

The superintendent of the Army Nurses Corps, Major Julia O. Flikke, Surgeon General's Office, Washington, D. C., gave an urgent call January 2 for three thousand five hundred immediate volunteer nurses to serve in army hospitals in military training camps, mostly in the southern part of the country. However, about 684 of them can be used in the Third Corps Area (Pennsylvania, Virginia, Maryland and the District of Columbia). The recruiting agent for the Army Nurses Corps is the American Red Cross, and although seventeen thousand qualified nurses are on the reserve list they have been accepting assignment to active duty slowly and perhaps as the result of their failure to realize, it was said, that the need is really acute.

### BARRACKS FOR WALTER REED HOSPITAL

Two barracks will be constructed to house reserve officers who will pursue special courses at Walter Reed General Hospital at the Army Medical Center in Washington from time to time in surgery and in other medical practice, each barrack to have a capacity of forty officers. A total of seventeen barracks will be built to house enlisted personnel ordered to Walter Reed for technical training as laboratory, roentgen ray and dental technicians, ward masters and ward nurses, and in other capacities. A mess hall and kitchen to accommodate seven hundred and fifty enlisted men will be constructed as part of a \$584,056 program authorized by the War Department on December 16.

### EQUIPMENT FOR PREVENTION OF ASPHYXIAL DEATH

The Society for the Prevention of Asphyxial Death, New York, has received notice from the British Red Cross Society in London that the equipment exhibited by the society at the New York World's Fair has been safely received. This society recently appealed for funds amounting to about \$4,000 to send this asphyxia prevention equipment to England.

The society has had designed also a special resuscitation unit for the treatment of the three stages of asphyxia (depression, spasticity and flaccidity) and had it assembled for oversea service. Each unit will cost \$150. The Society for the Prevention of Asphyxial Death is now making an appeal for funds to secure one thousand of these resuscitation outfits to prevent death from asphyxial accidents which occur as the result of air raids. Each outfit sent abroad will bear the name of the donor, be this an individual, a club, a hospital staff, a nurses' training school or a college or fraternity group. Those desiring to participate in thus extending relief for emergencies now occurring

in Britain should communicate at once with the Society for the Prevention of Asphyxial Death, 38 East Sixty-First Street, New York; telephone Regent 4-3515.

### CLASSES AT CARLISLE BARRACKS

The class of one hundred and seventy officers now at the Medical Field Service School at Carlisle Barracks, Pa., began its course Dec. 9, 1940 and finished January 11. Immediately thereafter another class of about two hundred officers started. The normal courses of several months have been suspended on account of the emergency, and in their place the school has short courses, averaging one month each, for newly commissioned reserve officers who have been ordered to active duty. The instruction covers only important subjects that are not taught in medical, dental or veterinary schools—map reading, military art, logistics (the science of transporting men and supplies), medical department administration, methods of training (officers and enlisted men), field sanitation, military preventive medicine, tactics and military law.

### CONFERENCE OF PSYCHIATRISTS

A conference of psychiatrists from various states was held in Washington, D. C., January 2-3. Clarence A. Dykstra, director of Selective Service, and Brig. Gen. Lewis B. Hershey, deputy director of Selective Service, presided at the first two sessions. Paul V. McNutt, Federal Security Administrator, spoke on "What We Expect of Psychiatry in the National Defense Program." Dr. James S. Plant, director of the Essex County (N. J.) Juvenile Clinic, discussed "The Psychiatric Challenge in Selective Service." Other speakers were Lewellys Barker, formerly chief of the medical service at Johns Hopkins University Hospital, Baltimore; Dr. Harry S. Sullivan of the William Alanson White Psychiatric Foundation; Drs. Winfred Overholzer, Roscoe W. Hall and Alexander Simon of St. Elizabeth's Hospital, Washington, D. C.; Dr. Lauren Smith of the Pennsylvania Institute; Dr. Spafford Ackerley of the University of Louisville School of Medicine, Louisville, Ky.; Dr. Dexter M. Bullard of Chestnut Lodge Sanitarium; Dr. Martin Cooley of the Veterans' Administration, and Lieut. Col. William C. Porter, M. C., U. S. Army. Guests at the conference included local draft board physicians from Virginia, Maryland, West Virginia, North Carolina, Delaware and Washington, D. C. According to the *Washington Star*, Col. Leonard G. Rowntree, newly appointed medical director of Selective Service, said that the general purpose of the conference was to create standards on a national basis for choosing the best type of man for military training. This is the first conference of a nationwide series to be held in different parts of the country.

## ARMY RESERVE OFFICERS ORDERED TO ACTIVE DUTY

### THIRD CORPS AREA

The following additional medical reserve corps officers had been ordered to extended active duty by the Commanding General, Third Corps Area, up to January 3. The Third Corps Area comprises the states of Pennsylvania, Virginia, District of Columbia and Maryland.

ARNAO, James, 1st Lieut., Philadelphia, Camp Shelby, Miss.  
BANEN, David Merton, Captain, Baltimore, Camp Blanding, Fla.  
BARKOFF, Samuel, 1st Lieut., Sykesville, Md., Fort George G. Meade, Md.  
BECKER, Philip Lawrence, 1st Lieut., Pittsburgh, Fort George G. Meade, Md.  
BERGER, Emanuel, 1st Lieut., Pittsburgh, Camp Shelby, Miss.  
BLOOM, Charles Henry, Captain, Altoona, Pa., Altoona Induction Board, Altoona, Pa.  
BOUCEK, Charles Michael, Captain, Pittsburgh, Fort Knox, Ky.  
BOUCEK, Richard John, 1st Lieut., Pittsburgh, Camp Blanding, Fla.  
BRIGULIO, Alfred Emanuel, 1st Lieut., Washington, D. C., Fort George G. Meade, Md.  
BUTLER, William Sullivan, 1st Lieut., Wellsboro, Pa., Fort Eustis, Va.  
CADY, Joseph Bishop, 1st Lieut., Sayre, Pa., Indiantown Gap, Pa.  
CAMERON, Donald Young, Captain, Mount Lebanon, Pa., Fort Monroe, Va.  
CAMPBELL, Otho Perry, 1st Lieut., White Stone, Va., Camp Blanding, Fla.  
CARBONETTA, Reno Raymond, 1st Lieut., Lancaster, Pa., Camp Lee, Va.  
CARSON, Winfield Bankerd, Jr., Captain, Pittsburgh, Camp Blanding, Fla.  
CHASE, William David, 1st Lieut., McLean, Va., Fort Eustis, Va.  
CHRISTMAN, Albert Henry, 1st Lieut., Emporium, Pa., Fort Eustis, Va.  
CLEAVER, Edgar Eugene, 1st Lieut., Palm, Pa., Camp Blanding, Fla.  
COHEN, Franklin Harry, 1st Lieut., Norfolk, Va., Camp Shelby, Miss.  
COHEN, Morris M., 1st Lieut., Pittsburgh, Fort Monroe, Va.  
CORRIGAN, Timothy Michael, 1st Lieut., Hazleton, Pa., Camp Blanding, Fla.  
CULEN, Baker William, 1st Lieut., State College, Pa., Camp Shelby, Miss.  
DAVIS, Jacob Ralph, 1st Lieut., Pittsburgh, Camp Blanding, Fla.  
DOUGHERTY, Francis Michael, 1st Lieut., Summit Hill, Pa., Camp Blanding, Fla.  
EDWARDS, Hugh Robertson, 1st Lieut., Newport News, Va., Camp Shelby, Miss.  
EISNER, Albert L., Captain, Monaca, Pa., Camp Pendleton, Va.  
ELLIOTT, Grant Roosevelt, Captain, Orange, Va., Camp Blanding, Fla.  
ENSMINGER, Chalmers Da Costa, Captain, York, Pa., Fort George G. Meade, Md.  
FAUDREE, Leslie Allen, 1st Lieut., Stanleytown, Va., Camp Blanding, Fla.  
FEAR, Jesse Gerard, 1st Lieut., Berwick, Pa., Camp Shelby, Miss.  
FITZGERALD, Edward Murray, 1st Lieut., Pittsburgh, Camp Blanding, Fla.  
FOSTER, Frederic James, 1st Lieut., Washington, D. C., Fort Benning, Ga.  
FRIEDMAN, Joseph, 1st Lieut., Westernport, Md., Fort George G. Meade, Md.  
FRIEND, Arthur, 1st Lieut., Dupont, Pa., Camp Blanding, Fla.

FRONCZEK, William Michael, 1st Lieut., Pittsburgh, Camp Blanding, Fla.  
GABRESKI, Thaddeus Stanley, 1st Lieut., Oil City, Pa., Camp Shelby, Miss.  
GOLDSTEIN, Ralph Leon, 1st Lieut., Renovo, Pa., Camp Shelby, Miss.  
GUENON, William Augustus, 1st Lieut., Greencastle, Pa., Camp Blanding, Fla.  
GRASS, Edward Jacob, Captain, Washington, D. C., Camp Shelby, Miss.  
HALL, Gordon Douglas, 1st Lieut., Dumbarton, Va., Camp Blanding, Fla.  
HAMMOND, Charles Pries, 1st Lieut., Lancaster, Pa., Camp Shelby, Miss.  
HARTWELL, Donald Clifford, 1st Lieut., Takoma Park, D. C., Camp Blanding, Fla.  
HAZLETT, Frank Dickerson, Captain, Waynesburg, Pa., Camp Shelby, Miss.  
HELLMAN, Leo Alfred, Captain, Port Alleghany, Pa., Camp Shelby, Miss.  
HELWIG, Frederick George, 1st Lieut., Allentown, Pa., Camp Blanding, Fla.  
HELZLSOUER, Wilbert James, 1st Lieut., Dravosburg, Pa., Camp Shelby, Miss.  
HESSION, Henry Monroe, 1st Lieut., Philadelphia, Camp Blanding, Fla.  
HOCKENBERRY, Ralph Emerson, 1st Lieut., Smethport, Pa., Camp Blanding, Fla.  
HOPEWELL, Edward Lee, 1st Lieut., Strasburg, Va., Camp Shelby, Miss.  
HULL, Logan Ben, 1st Lieut., Altoona, Pa., Camp Blanding, Fla.  
ITSCOTTZ, Seymour E., 1st Lieut., McKeesport, Pa., Camp Shelby, Miss.  
JACOBSON, Philip, 1st Lieut., Williamsport, Pa., Camp Shelby, Miss.  
KELLY, Thomas Joseph, 1st Lieut., Washington, D. C., Camp Blanding, Fla.  
LARGE, John Simpson, 1st Lieut., Somerset, Pa., Camp Blanding, Fla.  
MAHONEY, Vincent Paul, 1st Lieut., Connellsville, Pa., Fort Eustis, Va.  
MARKLE, Cyrus Painter, Jr., 1st Lieut., West Newton, Pa., Fort Eustis, Va.  
MATHER, Clayton Black, Captain, Drexel Hill, Pa., Fort George G. Meade, Md.  
MORSE, Edward Clarke, Major, Washington, D. C., Fort Eustis, Va.  
NAEGELI, Frank Delee, Jr., 1st Lieut., Philadelphia, Fort Eustis, Va.  
NOBLE, Nathan Morton, 1st Lieut., Philadelphia, Camp Pendleton, Va.  
PETER, Arnold Leo, 1st Lieut., Baltimore, Fort George G. Meade, Md.  
PLACE, Elmer Raymond, Captain, Skippack, Pa., Fort Eustis, Va.  
RIGGLE, Paul Phillips, Captain, Washington, Pa., Fort Myer, Va.  
RITTENHOUSE, Emory Arthur, 1st Lieut., Monongahela, Pa., Fort Myer, Va.  
ROGEL, Louis Frederick, 1st Lieut., Uniontown, Pa., Fort Monroe, Va.  
SAPIRA, Harry Albert, Captain, Elizabeth, Pa., Fort Monroe, Va.  
SEDWICK, Jack Donovan, 1st Lieut., Brockway, Pa., Fort Monroe, Va.  
SHAPIRO, Jerome Joseph, 1st Lieut., Richmond, Va., Camp Pendleton, Va.  
SIEGEL, Bernard, 1st Lieut., Philadelphia, Camp Pendleton, Va.  
SIMPSON, Allan James, Jr., 1st Lieut., McKeesport, Pa., Camp Shelby, Miss.  
SPECTOR, Martin, 1st Lieut., Philadelphia, Fort Jackson, S. C.  
SWISS, Adam George, 1st Lieut., Baltimore, General Dispensary U. S. Army, Baltimore.  
THOMPSON, Thomas Ewing, Jr., 1st Lieut., Avalon, Pa., Fort Belvoir, Va.  
WOOLHANDLER, Harry William, Captain, Erie, Pa., Fort Belvoir, Va.

### FOURTH CORPS AREA

The following medical reserve corps officers have been ordered to active duty by the Commanding General, Fourth Corps Area, since Dec. 27, 1940. The Fourth Corps Area comprises the states of Tennessee, North Carolina, South Carolina, Alabama, Georgia, Mississippi, Florida and Louisiana.

ADAMS, Daniel M., 1st Lieut., Panama City, Fla.  
BERMAN, Dave, 1st Lieut., Columbus, Ga., Camp Blanding, Fla.  
BOWIE, Eleazar R., Lieut. Col., New Orleans, Fort Benning, Ga.  
BROOK, Clarence L., 1st Lieut., Tuscaloosa, Ala., Camp Blanding, Fla.  
CAMP, Horton, 1st Lieut., Pittsboro, N. C.  
COLEMAN, Olon H., 1st Lieut., Jacksboro, Tenn., Camp Blanding, Fla.  
DAFFIN, Charles H., 1st Lieut., Jacksonville, Fla.  
DEAL, Albert M., 1st Lieut., Statesboro, Ga.  
DEPRIEST, Frederick E., 1st Lieut., Batesville, Miss.  
DRAMUS, William H., 1st Lieut., Selma, Ala.  
DIDCOCT, John W., 1st Lieut., Paris, Tenn.  
GIBSON, Rae B., 1st Lieut., Greeneville, Tenn., Fort Jackson, S. C.  
HENDRIX, Clive V., Captain, Oneonta, Ala.  
HERRON, Henry H., 1st Lieut., Bemis, Tenn., Camp Peay, Tenn.  
KAUFMAN, James K., 1st Lieut., Nashville, Tenn., Camp Peay, Tenn.  
KENDALL, John H., 1st Lieut., Richlands, N. C.  
KERAMIDAS, Theodore C., 1st Lieut., Winter Haven, Fla.  
KILLEFFER, John J., 1st Lieut., Chattanooga, Tenn.  
LARD, Earl L., 1st Lieut., Union, Miss., Fort McClellan, Ala.  
LYTLE, Carl S., 1st Lieut., Ocala, Fla.  
MCGRAW, Felix J., 1st Lieut., Birmingham, Ala.  
MCKELL, Thomas E., 1st Lieut., West Point, Miss., Camp Peay, Tenn.  
MCKEY, Earle S., Jr., 1st Lieut., Valdosta, Ga.

MILTON, John D., Captain, Miami, Fla.  
MULLINS, Julius H., 1st Lieut., Baton Rouge, La.  
NORMENT, Robert L., 1st Lieut., Fayetteville, N. C.  
OCHS, Louis, Jr., 1st Lieut., New Orleans, Fort Benning, Ga.  
PARKER, Paul H., 1st Lieut., Margaret, Ala., Camp Shelby, Miss.  
PARKS, Harry, 1st Lieut., Atlanta, Ga., Camp Stewart, Ga.  
PLUMMER, David E., 1st Lieut., Durham, N. C.  
PRICE, George W., Jr., 1st Lieut., Spartanburg, S. C., Camp Blanding, Fla.  
RICHARDSON, Guy C., Captain, Bristol, Tenn., Fort McClellan, Ala.  
RIZZO, Frank P., Major, Monroe, La.  
ROGERS, Hunter B., Captain, Miami, Fla., Camp Shelby, Miss.  
ROSENFELD, Abraham P., 1st Lieut., Dillon, S. C.  
RUFFIN, James S., Jr., 1st Lieut., Knoxville, Tenn., Camp Peay, Tenn.  
RUSSEL, John C., Jr., 1st Lieut., Cleveland, Miss., Camp Shelby, Miss.  
SADOVE, Max G., 1st Lieut., Savannah, Ga., Camp Blanding, Fla.  
SALLE, George F., 1st Lieut., Vanceboro, N. C., Carlisle Barracks, Pa., 1 month, then to Camp Lee, Va.  
SANDERS, Keith F., 1st Lieut., Kingstree, S. C., Camp Shelby, Miss.  
SAWYER, James L., 1st Lieut., Folkston, Ga.  
SHAW, Vaughan A., 1st Lieut., Daytona Beach, Fla.  
SHIPP, Larry G., 1st Lieut., Anniston, Ala., Camp Blanding, Fla.  
TEMPLES, Andrew K., 1st Lieut., Augusta, Ga.  
TEMPLETON, Clinton M., 1st Lieut., Augusta, Ga., Camp Shelby, Miss.  
WARRINER, George W., 1st Lieut., Birmingham, Ala.  
WARRINER, Richard B., 1st Lieut., Corinth, Miss.  
WILSON, George D., 1st Lieut., Kernersville, N. C., Camp Shelby, Miss.  
WORTH, Thomas C., 1st Lieut., Raleigh, N. C.  
WRIGHT, James C., Captain, Chattanooga, Tenn.  
YOUNG, Henry D., 1st Lieut., Bushnell, Fla.  
YOUNG, Joseph A., 1st Lieut., Newton, N. C.

**Relieved from Duty**

The following officers previously reported have been relieved from duty or their orders have been revoked:

BROOKS, Marshall, Jr., 1st Lieut., Atlanta, Texas.  
COLLINS, Braswell E., 1st Lieut., Waycross, Ga.  
FARRAR, Turley, 1st Lieut., Memphis, Tenn.  
GORDON, Joseph T., 1st Lieut., Pulaski, Tenn.  
HYER, Yeadon M., 1st Lieut., Darlington, S. C.  
KENDALL, Cyrus E., 1st Lieut., Madison College, Tenn.  
PARKER, Shepard, 1st Lieut., Shelby, N. C.

**SEVENTH CORPS AREA**

The following additional medical reserve corps officers had been ordered to active duty by the Commanding General, Seventh Corps Area, up to January 3. The Seventh Corps Area comprises the states of North Dakota, South Dakota, Minnesota, Nebraska, Iowa, Kansas, Missouri, Arkansas, and Wyoming.

BAKER, Roscoe Edward, Captain, Winigan, Mo., Carlisle Barracks, Pa.  
BROWN, Merle J., Captain, Davenport, Iowa, Carlisle Barracks, Pa.  
BURST, Emil Andrew, Captain, St. Louis, Camp Grant, Ill.  
CAVANOR, Frank Tracy, Captain, Minneapolis, Carlisle Barracks, Pa.  
CONLIN, Leo James, 1st Lieut., St. Paul, Carlisle Barracks, Pa.  
CORN, Henry Herman, 1st Lieut., Des Moines, Iowa, Carlisle Barracks, Pa.  
FRANK, Harold Joseph, 1st Lieut., New Prague, Minn., Carlisle Barracks, Pa.  
GARROW, Douglas Moore, 1st Lieut., St. Paul, Carlisle Barracks, Pa.  
HAINES, Diedrich Jansen, 1st Lieut., Des Moines, Iowa, Camp Grant, Ill.  
HALL, Durward Gorham, 1st Lieut., Springfield, Mo., Camp Grant, Ill.  
HANSEY, Samuel Albert, 1st Lieut., St. Louis, Camp Grant, Ill.  
HAYS, Albert Theodore, 1st Lieut., Minneapolis, Carlisle Barracks, Pa.  
HENRICH, Leo Charles, 1st Lieut., Omaha, Carlisle Barracks, Pa.  
HUGEL, Lawrence Eugene, 1st Lieut., North Platte, Neb., Carlisle Barracks, Pa.  
HUNTER, Martin Peters, 1st Lieut., Moberly, Mo., Camp Grant, Ill.  
HYDE, Marshall Earl, 1st Lieut., Augusta, Kan., Carlisle Barracks, Pa.  
KELLING, Jordan Albert, Captain, Waverly, Mo., Carlisle Barracks, Pa.  
LOTMAN, Harry Alfred, 1st Lieut., Lincoln, Neb., Carlisle Barracks, Pa.  
LYDDON, Donald Withers, 1st Lieut., St. Louis, Camp Grant, Ill.  
MARTIN, Melvin Cecil, Captain, Newton, Kan., Carlisle Barracks, Pa.  
McCARTY, Dale Charles, 1st Lieut., Anthony, Kan., Carlisle Barracks, Pa.  
McCOMAS, Marmaduke D., Captain, Courtland, Kan., Carlisle Barracks, Pa.  
MEANY, John Joseph, 1st Lieut., St. Louis, Camp Grant, Ill.

**EIGHTH CORPS AREA**

The following additional medical reserve corps officers had been ordered to active duty by the Commanding General, Eighth Corps Area, up to January 3. The Eighth Corps Area comprises the states of Colorado, Arizona, New Mexico, Oklahoma and Texas.

ADAMS, Freeman H., 1st Lieut., Phoenix, Ariz., Station Hospital, Fort Sill, Okla.  
ASHMORE, Alvin Jackson, 1st Lieut., Corpus Christi, Texas, Station Hospital, Fort Sam Houston, Texas.  
BARNACLE, Clarke H., Captain, Denver, Station Hospital, Fort Sam Houston, Texas.  
BARNES, Johnson Peyton, 1st Lieut., Houston, Texas, Station Hospital, Fort Crockett, Texas.  
BEVIL, Lamar C., Captain, Beaumont, Texas, Station Hospital, Fort Crockett, Texas.  
BISHOP, Calmes P., 1st Lieut., Picher, Okla.  
BLOCK, Harold M., Captain, Dallas, Texas.  
BRAU, John G., 1st Lieut., Dallas, Texas, Station Hospital, Fort Sam Houston, Texas.  
BROCK, Ernest D., Captain, Yucca, Ariz., Fort Bliss, Texas.  
BROWN, Charles H., Captain, Wichita Falls, Texas.  
BROWN, Robert N., 1st Lieut., Denver.  
BRYANT, George Calvin, Jr., 1st Lieut., Dallas, Texas.  
BULLARD, Ray Elva, Captain, Waco, Texas.  
CARSON, John M., 1st Lieut., Shawnee, Okla., Station Hospital, Fort Sill, Okla.  
CHILDERS, Marvin A., Jr., Captain, San Antonio, Texas.  
CLARK, Benjamin P., Captain, Okeene, Okla.  
CONTE, Raphael, 1st Lieut., Houston, Texas.  
DAILY, Robert W. L., 1st Lieut., Wichita Falls, Texas, Station Hospital, Fort Sam Houston, Texas.  
DATHE, Richard Arthur, 1st Lieut., Dallas, Texas, Station Hospital, Fort Sam Houston, Texas.  
DAY, Merriwether L., 1st Lieut., Phoenix, Ariz.  
DEATHERAGE, William R., Captain, Dallas, Texas.  
DELANEY, Albert Lindsay, Captain, Liberty, Texas, Station Hospital, Fort Crockett, Texas.  
DeLANGE, Arnett, 1st Lieut., Galveston, Texas.  
DETER, Russell Lee, 1st Lieut., Dallas, Texas, Station Hospital, Fort Sam Houston, Texas.

SMITH, Daniel L., Jr., 1st Lieut., Spartanburg, S. C.  
STATON, Leon R., 1st Lieut., Hayesville, N. C.

**CORRECTION**

**Lieut. Alexander F. Russell.**—In the Medical Preparedness section of THE JOURNAL, Dec. 28, 1940, page 2287, under the Fourth Corps Area, the name Ralph S. Russell, First Lieutenant, Ocala, Fla., should have been Alexander F. Russell, First Lieutenant, Dover, Tenn.

MEINBERG, William Henry, 1st Lieut., St. Louis, Camp Grant, Ill.  
MIDDLEMAN, Isadore Carl, Captain, St. Louis, Carlisle Barracks, Pa.  
MOBLEY, Hugh, 1st Lieut., Searcy, Ark., Carlisle Barracks, Pa.  
MULLIGAN, Arthur Montgomery, Captain, Brainard, Minn., Carlisle Barracks, Pa.  
NEDERHISER, Morgan Ira, 1st Lieut., Cascade, Iowa, Carlisle Barracks, Pa.  
POE, John Selden, 1st Lieut., St. Louis, Camp Grant, Ill.  
POTASHNICK, Robert, 1st Lieut., St. Louis, Camp Grant, Ill.  
RICHMOND, Paul Carlton, 1st Lieut., New Hampton, Iowa, Camp Grant, Ill.  
SALMON, David D., 1st Lieut., Little Rock, Ark., Carlisle Barracks, Pa.  
SANDRITTER, Gilbert Lee, 1st Lieut., Norfolk, Neb., Carlisle Barracks, Pa.  
SCHILLING, Robert Dean, 1st Lieut., Clayton, Mo., Carlisle Barracks, Pa.  
SETTLE, Emmett Bird, Captain, Rockport, Mo., Carlisle Barracks, Pa.  
SHERMAN, Kenneth Eugene, 1st Lieut., Sturgis, S. D., Carlisle Barracks, Pa.  
SIMONTON, Kinsey MacLeod, 1st Lieut., Rochester, Minn., Camp Grant, Ill.  
SMITH, Frederick Abbott, 1st Lieut., Rochester, Minn., Camp Grant, Ill.  
STERNHILL, Isaac, Captain, Council Bluffs, Iowa, Camp Grant, Ill.  
STILL, Richard Mathias, 1st Lieut., Lincoln, Neb., Camp Grant, Ill.  
STRATHERN, Carleton Schleuder, 1st Lieut., St. Peter, Minn., Camp Grant, Ill.  
SULEK, Arthur Edward, 1st Lieut., Cedar Rapids, Iowa, Carlisle Barracks, Pa.  
SWANSON, Paul Edgar, 1st Lieut., Virginia, Minn., Camp Grant, Ill.  
UIHLEIN, Alfred, 1st Lieut., Rochester, Minn., Camp Grant, Ill.  
VAUGHN, Louis Dysart, 1st Lieut., Rochester, Minn., Camp Grant, Ill.  
WAKEMAN, Everal Marion, 1st Lieut., Fowler, Kan., Carlisle Barracks, Pa.  
WETRICH, Max Franklin, 1st Lieut., West Des Moines, Iowa, Camp Grant, Ill.  
WICKS, Ralph Litton, 1st Lieut., Winterset, Iowa, Carlisle Barracks, Pa.

DONNELLY, Allen Dalton, 1st Lieut., Honey Grove, Texas.  
DOYLE, William Henry, Captain, Muskogee, Okla., Station Hospital, Fort Sill, Okla.  
ENGLAND, Myron C., 1st Lieut., Woodward, Okla., Station Hospital, Fort Sam Houston, Texas.  
ENGLISH, Otis W., Captain, Lubbock, Texas.  
ESPEY, James G., Jr., 1st Lieut., Trinidad, Colo.  
ETTER, Edward F., Captain, Sherman, Texas, Station Hospital, Fort Sam Houston, Texas.  
EWERT, William A., 1st Lieut., Kingsville, Texas.  
GALT, Sidney, Captain, Dallas, Texas, Station Hospital, Fort Sam Houston, Texas.  
GANDY, Daniel Truett, Major, Houston, Texas, Station Hospital, Fort Crockett, Texas.  
GARNETT, John Wilson, Jr., Captain, Fort Worth, Texas, Station Hospital, Fort Sill, Okla.  
GERSH, Isadore, 1st Lieut., Denver, Station Hospital, Fort Sill, Okla.  
GIBBENS, Murray E., 1st Lieut., Denver.  
GIERE, Carl N., 1st Lieut., El Paso, Texas.  
GLASIER, William Albert, 1st Lieut., Carlsbad, N. M., Fort Bliss, Texas.  
GLATHAR, Albert William, 1st Lieut., Pueblo, Colo., Fort Bliss, Texas.  
GONZALEZ, Saturnino M., 1st Lieut., Santa Fe, N. M.  
HARRISON, Ben F., Jr., 1st Lieut., Dallas, Texas.  
HAYES, Elmer R., 1st Lieut., Greenville, Texas.  
HAYNES, Elmer, 1st Lieut., Rusk, Texas, Station Hospital, Fort Sam Houston, Texas.  
HILL, Kenneth A., Major, Denver.  
HOWARD, Robert Bruce, 1st Lieut., Oklahoma City, Station Hospital, Fort Sam Houston, Texas.  
HUCHERSON, Denman Carter, 1st Lieut., Oklahoma City, Station Hospital, Fort Sam Houston, Texas.  
HUGHES, Sidney W., 1st Lieut., Brownwood, Texas, Station Hospital, Fort Crockett, Texas.  
HYSLOP, James R., 1st Lieut., El Paso, Texas, Station Hospital, Fort Sill, Okla.  
JAEHNE, Robert J., 1st Lieut., Austin, Texas.  
JAFFA, Bertram B., Captain, Denver.  
JANUARY, Harold L., 1st Lieut., Albuquerque, N. M., Station Hospital, Fort Crockett, Texas.  
JOHNSON, Emmett Root, 1st Lieut., Brush, Colo.

JONES, Dean Bigham, 1st Lieut., Dublin, Texas., Station Hospital, Fort Sam Houston, Texas.  
JONES, Ernest W., Captain, Kenedy, Texas.  
KAPLAN, Hyman J., Captain, Orange, Texas.  
KIMBALL, Merritt H., 1st Lieut., Denver.  
ROOTSEY, J. S., Captain, Houston, Texas.  
KROOVAND, William Harold, 1st Lieut., Oklahoma City.  
LAMB, Marvin, 1st Lieut., Jacksonville, Texas, Station Hospital, Fort Sill, Okla.  
LEGGETT, Milbourne Kerlic, 1st Lieut., Houston, Texas, Station Hospital, Fort Crockett, Texas.  
LEHMAN, Herman O., 1st Lieut., Portales, N. M.  
LO BELLO, Leon, 1st Lieut., Dallas, Texas, Station Hospital, Fort Sam Houston, Texas.  
LOVELESS, Robert Wells, 1st Lieut., Lamesa, Texas.  
LYONS, Dave J., Captain, Seminole, Okla.  
MAGRISH, Philip, 1st Lieut., San Antonio, Texas.  
MANSKE, Gerhard Rudolph, 1st Lieut., Texas City, Texas, Station Hospital, Fort Crockett, Texas.  
MANSUR, Harl D., Jr., 1st Lieut., Big Springs, Texas.  
MARIL, Joseph J., 1st Lieut., Oklahoma City, Station Hospital, Fort Sill, Okla.  
MARX, Melvin, Jr., Captain, Clarksville, Texas.  
MAXFIELD, James Robert, Jr., Captain, Albuquerque, N. M., Station Hospital, Fort Sill, Okla.  
McDougal, Luther Love, Jr., 1st Lieut., Paris, Texas, Station Hospital, Fort Sill, Okla.  
McFADDEN, Candour Alfred, 1st Lieut., Abilene, Texas, Fort Bliss, Texas.  
McGLONE, Frank, 1st Lieut., Denver, Station Hospital, Fort Sam Houston, Texas.  
McMILLAN, James M., 1st Lieut., Vinita, Okla., Station Hospital, Fort Sill, Okla.  
MILLER, Robert A., 1st Lieut., San Antonio, Texas.  
MONROE, M. L., 1st Lieut., Jasper, Texas.  
MONSALVO, Rudolph Nieves Orozco, Captain, San Antonio, Texas.  
MONTGOMERY, Eugene Porter, 1st Lieut., Boston.  
MONTGOMERY, William David, 1st Lieut., Dallas, Texas.  
MORGAN, Thomas L., 1st Lieut., Hobbs, N. M.  
MURPHY, Joseph B., 1st Lieut., Dallas, Texas.  
OAKES, Harold F., 1st Lieut., El Paso, Texas.  
PACKARD, Duan E., 1st Lieut., Kerrville, Texas.  
PALMER, Joseph Woodrow, 1st Lieut., San Antonio, Texas, Station Hospital, Fort Sam Houston, Texas.  
PATTERSON, Robert Thomas, 1st Lieut., Houston, Texas, Station Hospital, Fort Crockett, Texas.  
PERRY, Herbert Allen, 1st Lieut., Medical Lake, Wash., Fort Bliss, Texas.  
PETER, James R., 1st Lieut., Ennis, Texas, Fort Bliss, Texas.  
PEYTON, John Bailey, 1st Lieut., Dallas, Texas.  
POLSON, Donald A., 1st Lieut., Phoenix, Ariz.  
REITZ, Percy Allison, Captain, Pittsburg, Texas., Station Hospital, Fort Sill, Okla.  
RICHARDS, John T., 1st Lieut., Rockdale, Texas.  
RICHIE, George T., 1st Lieut., Denver.  
RILEY, Edgar Davis, 1st Lieut., Terrell, Texas, Fort Bliss, Texas.

ROBBINS, Jacob Ben, 1st Lieut., El Paso, Texas, Station Hospital, Fort Sam Houston, Texas.  
ROBINETT, James Bradley, Jr., 1st Lieut., Houston, Texas, Station Hospital, Fort Sill, Okla.  
ROUTON, Benjamin C., 1st Lieut., Oklahoma City.  
RUCKER, Ralph W., 1st Lieut., Bartlesville, Okla., Station Hospital, Fort Sill, Okla.  
SHADDOCK, Carroll Bitting, Jr., 1st Lieut., Beaumont, Texas, Station Hospital, Fort Sam Houston, Texas.  
SHIVERS, George Clausman, Captain, Colorado Springs, Colo.  
SMITH, Carlton E., 1st Lieut., Henryetta, Okla.  
SMITH, Haskell, 1st Lieut., Stillwater, Okla., Station Hospital, Fort Sill, Okla.  
STANSELL, Paul O., Captain, San Antonio, Texas.  
STEINBERG, F. William, 1st Lieut., San Antonio, Texas, Station Hospital, Fort Sill, Okla.  
STEVENSON, Walter H., Captain, El Paso, Texas.  
STONE, Joseph R., 1st Lieut., San Antonio, Texas, Station Hospital, Fort Sam Houston, Texas.  
TALKINGTON, Perry Clement, 1st Lieut., Dallas, Texas, Station Hospital, Fort Sam Houston, Texas.  
TAYLOR, William A., Captain, Mount Pleasant, Texas.  
TERRY, Robert T., Captain, Denver.  
TRIMBLE, Orman Hughes, 1st Lieut., Greenville, Texas, Station Hospital, Fort Sam Houston, Texas.  
VAN SICKLE, Rayburn Jefferson, 1st Lieut., Longview, Texas.  
WALKER, Glen H., 1st Lieut., Coolidge, Ariz., Fort Bliss, Texas.  
WALKER, Newton F., 1st Lieut., El Paso, Texas, Station Hospital, Fort Sam Houston, Texas.  
WALLACE, Henry G., 1st Lieut., Borger, Texas.  
WALTRIP, Powhatan M., Jr., 1st Lieut., Fort Worth, Texas, Station Hospital, Fort Sill, Okla.  
WATSON, Isaac Newton, 1st Lieut., Edmond, Okla., Station Hospital, Fort Sill, Okla.  
WEAVER, William Niebuhr, 1st Lieut., Muskogee, Okla., Station Hospital, Fort Sill, Okla.  
WILKOFF, Myron, 1st Lieut., Denver.  
WOOTEN, James Harbert, Jr., 1st Lieut., Fort Worth, Texas, Station Hospital, Fort Sill, Okla.

### Orders Revoked

Orders on the following officers previously reported have been revoked:

ANGUS, Howard, 1st Lieut., Lawton, Okla.  
BALDRIDGE, Max, 1st Lieut., Bowie, Texas.  
BUKOWSKI, Lucian M., Captain, Houston, Texas.  
BURNETT, Berry H., Lieut. Col., Englewood, Colo.  
DIMOND, Edgar A., 1st Lieut., Muskogee, Okla.  
GALLAGHER, C. A., 1st Lieut., Oklahoma City.  
LEIGHT, Sidney B., 1st Lieut., Denver.  
PRIDAY, Cedric, Major, Corpus Christi, Texas.  
PROSSER, Moorman P., 1st Lieut., Norman, Okla.  
SANFORD, Herbert M., 1st Lieut., Perryton, Texas.  
WAGNER, Gerald W., 1st Lieut., McKinney, Texas.

## NINTH CORPS AREA

The following additional medical reserve corps officers had been ordered to extended active duty by the Commanding General, Ninth Corps Area, up to January 4. The Ninth Corps Area comprises the states of Washington, Montana, Oregon, Nevada, Utah, California and Idaho.

ABDO, Francis J., 1st Lieut., Los Angeles, Fort Winfield Scott, Calif. (Temporary duty at Fort MacArthur pending final physical examination.)  
ADAMS, John Martin, Captain, Klamath Falls, Ore., Fort Lewis, Wash.  
ATKINSON, Russell E., 1st Lieut., San Bernardino, Calif., 19th Engineers, Presidio of Monterey, Calif.  
BREE, Donald W., 1st Lieut., Portland, Ore., Fort Lewis, Wash.  
CONNERS, T. P., 1st Lieut., Touasnet, Wash., Fort Lewis, Wash.  
COMORE, Jules B., 1st Lieut., San Francisco, Camp San Luis Obispo, Calif.  
COPELAND, Joseph, 1st Lieut., Visalia, Calif., 7th Division, Fort Ord, Calif.  
COVERSTONE, Vernon A., 1st Lieut., Spokane, Wash., Fort Lewis.  
CUNNINGHAM, Ralph T., 1st Lieut., Bakersfield, Calif., Fort MacArthur, Calif.  
EDELSTEIN, Maurice, 1st Lieut., Brentwood, Calif., Presidio of Monterey, Calif.  
FELDHIEYM, Jean S., 1st Lieut., San Francisco, Fort Lewis, Wash.  
FISHER, Arthur A., 1st Lieut., Lebanon, Ore., Fort Lewis, Wash.  
FREEMAN, Ralph W., 1st Lieut., Fillmore, Utah, Fort Stevens, Ore. (Temporary duty at Fort Douglas, Utah, pending final physical examination.)  
GORISHER, William M., 1st Lieut., Castle Gate, Utah. (Temporary duty at Fort Douglas, Utah, pending final type physical examination, then to Carlisle Barracks for one month, then to Fort Francis E. Warren, Wyoming, now in 7th Corps Area.)  
HARMON, Merle S., Captain, Montesano, Wash., Fort Worden, Wash.  
HEDGECOCK, Charles, 1st Lieut., Baker, Ore., Fort Lewis, Wash.  
HENNESSY, Harold R. Major, Yuba City, Calif., Northern California Military District.

HEMINGWAY, Max W., 1st Lieut., Bend, Ore., Fort Lewis, Wash.  
LIGHTBURN, William J., Captain, Palouse, Wash., Fort Lewis, Wash.  
LITTLEHALES, Charles E., 1st Lieut., Portland, Ore., 7th Division, Fort Ord, Calif.  
LOMAS, Jack B., 1st Lieut., Los Angeles, Presidio of Monterey, Calif.  
LUND, Grant V., 1st Lieut., North Hollywood, Calif., Fort MacArthur, Calif.  
MERKEL, Emil E., 1st Lieut., Los Angeles, Presidio of Monterey, Calif.  
MOSS, George L., 1st Lieut., Santa Ana, Camp McQuaide, Calif.  
NASH, Frank P., 1st Lieut., Townsend, Mont., Fort Stevens, Ore. (Temporary duty at Fort George Wright, Wash., pending final physical examination.)  
OLSON, Oscar C., 1st Lieut., Mason City, Wash., Fort Lewis, Wash.  
OLSON, William A., 1st Lieut., Los Angeles, Hearst Ranch, Jolon, Calif.  
OREDSON, Gustaf A., 1st Lieut., Kimberly, Nev., Fort Lewis, Wash.  
RILEY, John B., 1st Lieut., Sedro Woolley, Wash., Fort Stevens, Ore.  
SCHWARTZ, Simon D., 1st Lieut., Beverly Hills, Calif., 7th Division, Fort Ord, Calif.  
SLOAN, Leonard N., Major, Los Angeles, Fort Scott, Calif.  
SORENSEN, Edward J., 1st Lieut., Beverly Hills, Calif., Fort MacArthur, Calif.  
STEHLI, Charles C., 1st Lieut., Los Angeles, Fort Scott, Calif.  
STEWART, Joseph Byron, 1st Lieut., Portland, Ore., Fort Lewis, Wash.  
TAYLOR, Edward D., 1st Lieut., Centralia, Wash., Fort Lewis, Wash.  
WHITTAKER, Thomas W., 1st Lieut., Los Angeles, Presidio of Monterey, Calif.  
WICAL, Elvin A., 1st Lieut., Los Angeles, Camp McQuaide, Calif.  
YOST, Charles W., 1st Lieut., Portland, Ore., 7th Division, Fort Ord, Calif.  
YUSKIS, Anton S., 1st Lieut., San Diego, Calif., 7th Division, Fort Ord, Calif.

### Relieved

OSGOOD, Samuel B., 1st Lieut., ordered to extended active duty, Sept. 30, 1940, at Presidio of Monterey, Calif., relieved from duty December 20.

### Resigned

WILEY, James W., 1st Lieut., ordered to extended active duty, Nov. 14, 1940, at Fort Worden, Wash.; resigned December 24.

# ORGANIZATION SECTION

## MEDICAL LEGISLATION

### STATE MEDICAL LEGISLATION

#### Massachusetts

*Bills Introduced.*—S. 66 proposes to grant to a registered nurse caring for a person injured through the negligence of another a lien on all rights of action, suits, claims, counterclaims or demands accruing to the injured person because of his injuries. H. 54 proposes to permit any judge in enumerated courts to commit to the McLean hospital or to a private licensed institution a person so addicted to the intemperate use of barbituric acid and its derivatives as to have lost the power of self control. H. 114, to amend the medical practice act, proposes to require every licensed physician annually during December to register with the board of registration in medicine and at that time to pay a fee of \$2. H. 115, to amend those provisions of the medical practice act prohibiting a person from entering on or continuing in the practice of medicine until he has recorded with the clerk of the town where he has or intends to have an office his certificate of registration, proposes that (1) the town clerk shall certify on the face of the certificate that the recording required by law has been made, (2) the physician shall display the certificate so certified in a conspicuous place in his office and (3) a person rendering medical service without recording his certificate as here required shall recover no compensation therefor. H. 116 proposes to create a commission, consisting of a senator, three representatives and three physicians, to make an investigation and study of the advisability of requiring special qualifications of all physicians who engage in the practice of surgery and to file its recommendations with the clerk of the house of representatives on or before the first Wednesday of December 1942. H. 122 proposes to require the clerk or registrar of each city or town to give to persons who file notice of intention to marry such literature concerning gonorrhea and syphilis and the importance of premarital examination as may be furnished for that purpose by the state department of public health. H. 134 proposes to make various changes in the laws relating to food and drugs so as to make them conform substantially with those provisions of the Federal Food, Drug and Cosmetic Act pertaining to foods and drugs. H. 130 proposes to prohibit the retail sale or distribution of aminopyrine, cinchophen, barbituric acid or derivatives of those substances, except on the prescription of a physician, dentist or veterinarian.

### MEDICAL BILLS IN CONGRESS

*Bills Introduced.*—S. 193, introduced by Senator Murray, Montana, proposes to promote the general welfare by enabling the several states to make more adequate provision for compensation for disability or death of workers from silicosis or other dust diseases, by providing for cooperation with the several states. The Secretary of Labor will be charged with the duty of administering the provisions of the act. S. 194, introduced by Senator Murray, Montana, proposes to authorize research by the United States Public Health Service with respect to the cause, diagnosis and treatment of dental diseases. S. 195, introduced by Senator Murray, Montana, proposes to impose additional duties on the United States Public Health Service in connection with the investigation, treatment and control of tuberculosis. H. R. 5, introduced by Representative Smith, West Virginia, proposes to authorize the Secretary of Interior to make or cause to be made certain inspections and investigations in coal mines for the purpose of obtaining information relating to health and safety conditions, accidents and occupational diseases. H. R. 70, introduced by Representative Elliott, California, proposes to promote the national health through the prevention and control of tuberculosis among migrants. H. R. 150, introduced by Representative Tenerowicz, Michigan, proposes to permit deductions for income tax purposes of physician's and dentist's fees, hospital and funeral expenses. H. R. 577, introduced by Representative Fitzpatrick, New York, proposes to amend the Social Security Act so as to provide for the payment of benefits to permanently and totally disabled individuals. H. R. 584, introduced by Representative Fulmer, South Carolina, proposes to promote the national health and welfare through appropriation of funds for the construction of hospitals. This bill is identical with the Wagner-George hospital construction bill as introduced in the Seventy-Sixth Congress. H. R. 992, introduced by Representative Myers, Pennsylvania, proposes to extend the federal old age benefit provisions of the Social Security Act to certain nurses in respect to their employment outside of religious, charitable and nonprofit institutions. H. R. 1052, introduced by Representative Tolan, California, proposes that chiropractors be permitted to render treatment to beneficiaries of the United States Employees Compensation Act.

## OFFICIAL NOTES

### RADIO BROADCASTS

"Doctors at Work" is the title of the sixth annual series of dramatized radio programs being presented by the American Medical Association and the National Broadcasting Company.

The series opened Wednesday, Nov. 13, 1940 and will run for thirty consecutive weeks, closing with a broadcast from the A. M. A. meeting at Cleveland on June 4. The program is scheduled for 10:30 p. m. eastern standard time (9:30 central, 8:30 mountain, 7:30 Pacific time) over the Blue network, other N. B. C. stations and Canadian stations.

The programs are broadcast on what is known in radio as a sustaining basis; that is, the time is furnished gratis by the radio network and local stations and no revenue is derived from the programs. Therefore, local stations may or may not take the programs, at their discretion, except those stations which are owned and operated by the National Broadcasting Company.

Some radio stations may not be able to broadcast the program at the regular time at which it is scheduled and may transcribe and broadcast it at a different hour or even on another day. It is advisable therefore to verify the time of the broadcast by

reference to local newspapers or by telephoning the local Blue network stations.

The programs will dramatize what modern medicine offers the individual in the way of opportunities for better health and the more successful treatment of disease. Incidental to this main theme the programs will explain the characteristics of the different fields of modern medicine and its specialties.

Descriptive posters for local distribution may be had gratis from the Bureau of Health Education, American Medical Association, 535 North Dearborn Street, Chicago. Program titles will be announced weekly in *THE JOURNAL* and monthly in *Hygieia*, the Health Magazine.

Tickets are available for each broadcast. Address the Bureau of Health Education, American Medical Association, 535 North Dearborn Street, Chicago. Tickets are free, but a stamped self-addressed envelop should accompany requests.

The next three programs to be broadcast, together with their dates and titles, are as follows:

- January 22. Blocking Pain.
- January 29. Deeper Than It Looks.
- February 5. New Faces For Old.



## Medical News

(PHYSICIANS WILL CONFER A FAVOR BY SENDING FOR THIS DEPARTMENT ITEMS OF NEWS OF MORE OR LESS GENERAL INTEREST: SUCH AS RELATE TO SOCIETY ACTIVITIES, NEW HOSPITALS, EDUCATION AND PUBLIC HEALTH.)

### COLORADO

**Annual Midwinter Clinics—Refresher Courses.**—The Colorado State Medical Society will hold its annual midwinter clinics, the ninth, in Denver February 5-7. The guest lecturers will include:

Dr. Ralph Bowen, Houston, Texas, pediatrics.  
Dr. James T. Case, Chicago, radiology.  
Dr. Robert L. Faulkner, Cleveland, obstetrics and gynecology.  
Dr. Idys Mims Gage, New Orleans, general surgery.  
Dr. Chevalier L. Jackson, Philadelphia, otolaryngology.  
Dr. William S. Middleton, Madison, Wis., general medicine.  
Dr. Oscar L. Miller, Charlotte, N. C., orthopedics.  
Dr. Reed M. Nesbit, Ann Arbor, Mich., genito-urology.

A speaker from the U. S. Army Medical Corps will lecture on military medical subjects. Evenings will be devoted to a smoker, a symposium on cardiovascular-renal disease conducted by the guest speakers and a dinner dance. Two refresher courses, each for two full days, will be given in Denver February 3-4, immediately preceding the clinics, under the direction of the state medical society. One on "Disorders of the Heart and Circulatory System" will be given at the University of Colorado School of Medicine and hospitals, and the other, on "Diagnosis and Treatment of Fractures," will be given at the Denver General Hospital. There will also be an evening symposium on special fracture problems.

### CONNECTICUT

**Psittacosis Reported.**—According to *Public Health Reports*, Dr. Stanley H. Osborn, Hartford, commissioner of health of Connecticut, reported, December 9, one case of psittacosis in a patient who became ill November 2. Her physician suspected psittacosis because a recently purchased parakeet, received in Springfield, Mass., from a pet shop in California in October, had been ill a few days prior to the onset of illness of the patient.

### GEORGIA

**Endowment for Chair in Surgery.**—Emory University School of Medicine, Atlanta, has been given \$100,000 by the Joseph B. Whitehead Foundation to endow further the Joseph B. Whitehead chair in surgery, newspapers report. An additional \$16,500 was given to the medical school for use in connection with the chair, in memory of Conkey P. Whitehead, who died in November. The foundation was established after the death of Joseph B. Whitehead Jr., who willed his estate for the support of philanthropic and educational enterprises in the Atlanta area as a memorial to his father, Joseph B. Whitehead, one of the founders of the Coca-Cola Bottling Company. The foundation created the professorship in 1939 with an initial gift of \$250,000. In 1940 trustees of the foundation voted that about \$286,000 of its funds be distributed to Atlanta charitable and educational institutions before Christmas, the gifts to the university forming a part of this total.

### IDAHO

**Personal.**—Dr. Hugh F. Stanton, St. Genevieve, Mo., has been appointed director of the Central Idaho health unit to succeed Dr. Max B. McQueen, Lewiston, who has been called to active duty with the U. S. Army.—Dr. Richard D. Simonon, Boise, captain, medical reserve corps, U. S. Army, has been chosen to be selective service medical officer for the state. He will supervise the ten medical advisory boards throughout the state and the forty-eight local examining physicians.

### ILLINOIS

**Society News.**—The Henry County Medical Society was addressed in Kewanee recently by Drs. Leo K. Campbell and Channing W. Barrett, Chicago, on "Benefits and Dangers of Reducing" and "Preservation and Restoration of the Pelvic Floor" respectively.—Dr. Ralph C. Brown, Chicago, discussed "Chronic Ulcerative Colitis" before the Sangamon County Medical Society in Springfield, December 5.

### Chicago

**The Mayo Lecture.**—Dr. Stuart W. Harrington, Rochester, Minn., will deliver the annual Mayo Lecture in the library of Northwestern University Medical School, February 10. His subject will be "Diaphragmatic Hernia." This is considered the 1940 lecture.

**Fellowship for Study in Rheumatic Fever.**—Dr. Paolo Ravenna of Michael Reese Hospital will receive the first fellowship given by trustees of the Chicago Heart Association in memory of Morris Fishbein Jr. for research into the causes of rheumatic fever. The memorial fund was started in 1929 after the son of Dr. Morris Fishbein, Editor of *THE JOURNAL*, died of rheumatic fever. Dr. Ravenna graduated at Regia Università di Torino Facoltà di Medicina e Chirurgia in 1932. He was licensed to practice medicine in New York in 1940.

### IOWA

**Lester Tilton Cited on Contempt Charge.**—Lester Tilton, Clinton, a cancer quack who had no medical or pharmaceutical training, has been cited for alleged contempt of court because he was violating a decree restraining him from practicing medicine. He was ordered to appear in the district court January 21 by Judge Frank Kelsey, the *Davenport Times* reported December 21. In 1934 a permanent injunction restraining him from practicing medicine was obtained by the state, it was reported. It was stated that while he did not have a license to practice medicine he had worked up a large cancer-cure business. Earlier in that year Tilton began serving a term of thirty days in the Scott County Jail for nonpayment of a fine of \$1,000 imposed in federal court at Des Moines for violation of the federal Food and Drugs Act. Originally from Clinton, Tilton for many years exploited an alleged cure for cancer. He had an "institute" in Clinton where he treated at different times cancer, tuberculosis and syphilis. In 1933 Tilton was sentenced to serve from one to five years in the penitentiary and fined \$2,000 for conspiracy to violate the Illinois medical practice act.

### MASSACHUSETTS

**Professors Dam and de Hevesy Come to Harvard.**—Harvard University, Cambridge, announces that Prof. Henrik Dam, Biochemical Institute, University of Copenhagen, has been appointed Cutter lecturer on preventive medicine at the Harvard Medical School, Boston, for the current academic year and will lecture January 30 on vitamin K. Prof. George de Hevesy of the University of Copenhagen has been appointed the Dunham lecturer at Harvard for the current academic year and will deliver a series of lectures on "Application of Radioactive Isotopes to Biological Problems," beginning April 28. Professor de Hevesy discovered the element "hafnium" and introduced the application of isotopes as indicators in chemistry. These lectures are open to members of the medical profession and other interested professional persons.

### MICHIGAN

**Society News.**—Dr. Frank H. Bethell, Ann Arbor, discussed "Anemias Related to Nutritional Deficiencies with Particular Reference to Pregnancy" before the Genesee County Medical Society in Flint, January 7.—Dr. Howard T. Karsner, Cleveland, addressed the Wayne County Medical Society, Detroit, January 6, on "Ovarian Tumors with Hormonal Sexual Dysfunction." Dr. Albert M. Snell, Rochester, Minn., addressed the society January 13 on "Recent Studies on Hepatic Disease."

**Kellogg Foundation Creates New Post.**—Dr. Robert B. Harkness, director of the Barry County Health Department, Hastings, has been appointed assistant field director of the W. K. Kellogg Foundation, a newly created position. Dr. Harkness will take up his new work in May. He will be succeeded in Barry County by Dr. John K. Altland, Traverse City, director of the Grand Traverse County Health Department. Dr. Harkness will assist Dr. Matthew R. Kinde, Battle Creek, field director, in administering the educational activities and services in the seven counties which make up the foundation's health project.

### MINNESOTA

**Lectureship in Honor of Dr. Wright.**—The Twin City Urological Society has created an annual lectureship bearing the name of the late Dr. Franklin R. Wright. Although established just before Dr. Wright's recent death, announcement of the lecture has just appeared in the *Bulletin* of the Minnesota Medical Foundation. Dr. Wright had both medical and dental

degrees. He had been since 1896 a member of the faculty of the University of Minnesota Medical School, Minneapolis, until 1936, when he retired as associate professor of urology emeritus.

**Society News.**—The Ramsey County Medical Society, St. Paul, devoted its December 30 meeting to a symposium on fractures. The speakers were Drs. George A. Williamson, Stewart W. Shimonek, Alexander R. Colvin, Carl C. Chatterton and Victor P. Hauser. —Dr. Albert M. Snell, Rochester, discussed "Pancreatic Lithiasis" before the Minnesota Academy of Medicine, St. Paul, December 11. —Dr. Adelbert Louis Dippel, Minneapolis, discussed "X-Ray Pelvimetry" before the Hennepin County Medical Society, Minneapolis, December 18. —Dr. Harry P. Smith, Iowa City, addressed the Minnesota Pathological Society, December 17, on "The Coagulation of Blood with Special Reference to Vitamin K Therapy." —The Minnesota Society of Obstetrics and Gynecology was addressed in Duluth, December 14, among others, by Drs. William A. Coventry, Duluth, on "Actinomycosis of the Ovary"; Claude J. Ehrenberg, Minneapolis, "A Case of Severe Dysmenorrhea and Sterility Effectively Treated with Pranone," and James R. Manley, Duluth, "Intravenous Use of Ergotrate in the Third Stage of Labor."

### NEBRASKA

**Promotions at the University of Nebraska.**—Promotions recently announced at the University of Nebraska College of Medicine, Omaha, include:

Dr. William P. Haney, to be assistant professor of otorhinolaryngology.  
Dr. Charles W. McLaughlin Jr., assistant professor of surgery.  
Dr. Ernest L. MacQuiddy, associate professor of internal medicine.  
Dr. Willson B. Moody, associate professor of medicine.  
Dr. Reuben Allyn Moser, associate professor of internal medicine.  
Dr. George E. Robertson, assistant professor of pediatrics.  
Dr. Chester H. Waters, professor of surgery.

### NEW JERSEY

**Society News.**—Brig. Gen. Shelley U. Marietta, assistant surgeon general, U. S. Army, and commanding officer of Walter Reed General Hospital, Washington, D. C., addressed the Essex County Medical Society, Newark, January 9, on "Medical Preparedness for Military Emergency." —Dr. Henry W. Cave, New York, addressed a stated meeting of the Academy of Medicine of Northern New Jersey, Newark, January 16, on "Cancer of the Colon." —Dr. Robert H. Ivy, Philadelphia, spoke on "Surgical Conditions of the Face, Mouth and Jaws" at a meeting of the Atlantic County Medical Society, Atlantic City, January 10. —Dr. William D. Stroud, Philadelphia, addressed the Camden County Medical Society, Camden, January 7, on "Treatment of Cardiovascular Disease."

### NEW YORK

**Rochester Water Supply Polluted.**—A valve opened by mistake allowed polluted water from the Genesee River to enter the drinking water supply in Rochester for about sixteen hours, December 11, *Health News* reports. Steps to prevent outbreaks of water-borne illness were taken by health authorities, including typhoid vaccine, sufficient for treatment of 72,000 persons, shipped from the central state laboratory in Albany. Emergency chlorinators were used, and citizens were warned by radio, telephone and newspapers to boil the water. The Rochester General Hospital reported that 38 patients had symptoms of gastroenteritis that could be attributed to the contaminated water. Forty nurses were affected, with twenty-seven off duty at one time. It was estimated that more than 1,000 persons consulted physicians for mild gastroenteritis. No typhoid had been reported up to December 31.

### New York City

**Dr. Williams to Lecture on Diet.**—Robert R. Williams, Sc.D., chemical director of the Bell Telephone Laboratories, will deliver a lecture before the Greater New York Dietetic Association, February 4, on "The Evolution of Man's Dietary Requirements." Dr. Williams is known especially for his research on vitamin B. In 1938 he received the Willard Gibbs Medal of the Chicago section of the American Chemical Society in recognition of his work in the isolation and later synthesis of the vitamin.

**Social Hygiene Week Activities.**—The bureau of social hygiene of the New York City Department of Health will present an extensive program of educational activities for physicians, medical students, nurses, laboratory and public health workers during "Social Hygiene Week," January 29 to February 6. There will be all day programs at the health department building January 29, 30 and 31, and one including

special events for the public February 6. In addition there will be an evening meeting at the New York Academy of Medicine, February 4, and an all day social hygiene conference at the Hotel Astor on February 5.

**Society News.**—Dr. Malcolm Goodridge was elected president of the New York Academy of Medicine for a term of two years at a meeting, December 5, and Dr. Henry W. Cave, vice president for a term of three years. —Capt. Edward C. White, Medical Corps, U. S. Navy, addressed the Medical Society of the County of New York, December 23, on "Medical Preparedness in the Navy," and Col. Frank W. Weed, Medical Corps, U. S. Army, "The Medical Department of the Expanded Army." —Drs. Currier McEwen, Daniel Murray Angevine and Haig H. Kasabach presented a symposium on arthritis before the New York Roentgen Society, December 16.

### PENNSYLVANIA

**Society News.**—Dr. William Wayne Babcock, Philadelphia, addressed the annual meeting of the Lycoming County Medical Society, Williamsport, January 10, on "Current Medicosurgical Topics." Dr. Nathan B. Van Etten, New York, President of the American Medical Association, spoke at the annual banquet on "An American Health Program." Drs. Babcock and Francis F. Borzell, Philadelphia, president of the Medical Society of the State of Pennsylvania, made brief addresses. —Dr. Leo D. O'Donnell, Pittsburgh, addressed the Washington County Medical Society, Washington, January 8, on "Injuries to the Knee Joint."

### Philadelphia

**Lectures of the College of Physicians.**—Lectures to be presented before the College of Physicians of Philadelphia during the remainder of the year will be as follows:

Dr. Thomas T. Mackie, New York, Studies in Ulcerative Colitis, the Mary Scott Newbold Lecture, February 5.  
Dr. Ernest W. Goodpasture, Nashville, Tenn., The Cell-Parasite Relationship in Bacterial and Virus Diseases, the Alvarenga Prize Lecture, March 5.  
Dr. George L. Streeter, Baltimore, New Data on Embryogenesis in Monkey and Man, the Nathan Lewis Hatfield Lecture, April 2.  
Henry F. Vaughan, Dr.P.H., Detroit, The Way of Public Health, the James M. Anders Lecture, May 7.

### Pittsburgh

**University to Have Cyclotron.**—A gift of \$50,000 has been presented to the University of Pittsburgh for the construction of a cyclotron, the atom-smashing machine, in a special building near the medical center on O'Hara Street under the direction of Alexander J. Allen, Ph.D., associate professor of physics. Construction is expected to take about one year. Research projects now in progress at the university which have need for the cyclotron include cancer research, vitamin research and animal nutrition, studies of fertilized egg cells, the physics of metals and various biophysical researches.

### TEXAS

**Gift to Establish Serum Center.**—A gift of \$10,000 for the establishment of a blood, plasma and serum center at Baylor Hospital, Dallas, presented by Dr. and Mrs. Stanley J. Seeger, Milwaukee, was announced on December 25. The gift was made through the Southwestern Medical Foundation, of which Dr. Edward H. Cary, Dallas, is president, and will be a memorial to Mrs. Seeger's father, the late William Buchanan of Texarkana. The new center will expand the present activities of the hospital in preparing blood and plasma for transfusions. At the time the Seeger gift was announced, Dr. Cary suggested that blood be collected from volunteers to be shipped to England through the Dallas chapter of the British War Relief Society. Dr. Seeger is chairman of the Council on Industrial Health of the American Medical Association.

**Dallas Spring Clinical Conference.**—The thirteenth Annual Spring Clinical Conference of the Dallas Southern Clinical Society will be held at the Hotel Adolphus, Dallas, March 17-20. The honor guests will be:

Dr. Clifford J. Barborka, associate in medicine, Northwestern University Medical School, Chicago.  
Dr. William E. Chamberlain, professor of radiology and roentgenology, Temple University School of Medicine, Philadelphia.  
Dr. Harry Goldblatt, professor of experimental pathology and associate director, Institute of Pathology, Western Reserve University School of Medicine, Cleveland.  
Dr. Leland S. McKittrick, instructor in surgery, Harvard Medical School, Boston.  
Dr. Norman F. Miller, professor and head of the department of obstetrics and gynecology, University of Michigan Medical School, Ann Arbor, Mich.  
Dr. John J. Morton, professor of surgery, University of Rochester School of Medicine and Dentistry, Rochester, N. Y.

Dr. Henry G. Poncher, associate professor of pediatrics, University of Illinois College of Medicine, Chicago.

Dr. Jam's C. Sargent, clinical professor and director of the division of urology, Marquette University School of Medicine, Milwaukee.

Dr. Marion B. Sulzberger, assistant clinical professor of dermatology and syphilology, New York Post-Graduate Medical School, Columbia University, New York.

Dr. Derrick T. Vail Jr., professor and head of the department of ophthalmology, University of Cincinnati College of Medicine, Cincinnati.

Dr. Soma Weiss, Hersey professor of the theory and practice of physic, Harvard Medical School, Boston.

Dr. Fletcher D. Woodward, professor of diseases of the ear, nose and throat, University of Virginia Department of Medicine, Charlottesville.

## VIRGINIA

**New Medical College Hospital Dedicated.**—The Medical College of Virginia, Richmond, dedicated a new six hundred bed hospital on December 5, which was Founders Day at the college. The dedicatory exercises were held in the Monumental Episcopal Church near the college, with Col. E. W. Clark, commissioner of public works of the Public Works Administration, as the principal speaker. William T. Sanger, L.H.D., president of the college, presided and the speakers included Gov. James H. Price; Dr. Douglas Vanderhoof, Richmond, chairman of the executive committee board of visitors; Dr. Walter L. Bierring, Des Moines, Iowa, former President of the American Medical Association; Dr. Walter B. Martin, Norfolk, president of the Medical Society of Virginia; Harvey E. Jordan, Ph.D., dean, University of Virginia Department of Medicine, Charlottesville; Mr. M. Haskins Coleman Jr., secretary, Richmond Hospital Council, and Dr. Lewis E. Jarrett, director of the hospital division of the college. Rev. George Ossman, rector of the Monumental Episcopal Church, delivered the invocation and the benediction. The new hospital building, said to be the largest steel supported structure in the state, cost \$2,500,000. Part of the cost was provided by a grant of \$1,144,800 from PWA. The remainder came from the state, gifts and loans. The construction is in the form of a Maltese cross with the utility services in the center and the rooms for patients in the wings. By this arrangement wards and rooms have outside exposure. Teaching patients are to be segregated from private patients by the provision of separate entrances and lobbies. Equipment has been installed for air conditioning, and in the beginning the first and eleventh floors (the operating floors) will be cooled in summer. Two new services, neuropsychiatry and contagious diseases, have been provided for in the hospital. A landmark air beacon, constructed to government specifications, has been placed on the roof.

## GENERAL

**Examinations in Obstetrics and Gynecology.**—The American Board of Obstetrics and Gynecology announces that general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted at Cleveland from May 28 to June 2 prior to the annual session of the American Medical Association. Application for admission to Group A, Part II, examinations must be filed with the secretary not later than March 1. Formal notice of time and place will be sent to candidates in advance of the dates. Candidates for reexamination must apply to the secretary before April 15. Application forms and information may be obtained from the secretary, Dr. Paul Titus, 1015 Highland Building, Pittsburgh (6).

**Publications of the Children's Bureau.**—A directory of state, county and municipal training schools caring for delinquent children in the United States has been published by the Children's Bureau, U. S. Department of Labor. The section on state schools lists 115 institutions in the forty-eight states, the District of Columbia, Hawaii and Puerto Rico. The section on county and municipal schools lists forty-three that reported care of delinquent children following court disposition. Detention homes and other institutions reported as providing only temporary care are excluded. The population of the state schools, June 30, 1939, was 28,652 and that of the county and municipal ones was 3,945. Another recent publication of the bureau is the Proceedings of the White House Conference on Children in a Democracy held in Washington, Jan. 18-20, 1940, issued as Children's Bureau Publication 266.

**Prevention of Blindness—Annual Meeting.**—Mr. Mason H. Bigelow, a New York attorney, was elected president of the National Society for the Prevention of Blindness at the annual meeting in New York, December 12. He succeeds Mr. William Fellowes Morgan, who retired after serving the entire twenty-five years of the society's history. Mr. Morgan will have the title of president emeritus. Dr. Edward C. Ellett,

Memphis, was elected a vice president to fill the vacancy left by the recent death of Dr. Francis Park Lewis, Buffalo. The program of the meeting was "The Heritage Left to Coming Generations by Dr. Park Lewis," with Drs. Elliott B. Hague, Buffalo, and Ellice M. Alger, New York, Mr. Lewis H. Carris, general director of the society, and Mr. Charles Franchot, New York attorney, as the speakers. The society recently moved its headquarters with other members of the National Health Council to 1790 Broadway.

**Sectional Meeting on Ear, Nose and Throat.**—The Western Section of the American Laryngological, Rhinological and Otological Society will meet in San Francisco, February 1-2. A symposium on therapy of diseases of the ear, nose and throat will be presented the first day by Drs. Walter P. Covell, San Francisco, on vitamin therapy; Maurice L. Tainter, San Francisco, pharmacology of vasoconstrictor drugs; Edwin E. Osgood, Portland, Ore., chemotherapy; Leo Henry Garland, San Francisco, roentgen therapy, and Karl F. Meyer, Ph.D., San Francisco, serum therapy. Among speakers the second day will be:

Dr. H. Brodie Stephens, San Francisco, Operative Treatment of Carcinoma of the Esophagus.

Dr. Howard A. Brown, San Francisco, Post-Traumatic Syndrome of Head Injuries.

Dr. Henry J. Profant, Santa Barbara, Calif., Brain Abscesses with Recovery.

**Epidemic of Influenza Moves Eastward.**—The U. S. Public Health Service reports that the epidemic of influenza, prevalent for some weeks in the Western states, is moving eastward. A total of 77,144 cases was reported for the country as a whole on January 4. The number of cases is below the 1932 peak of 90,000 and the 1929 maximum of 195,000, according to the New York Times. Prevalence in California reached a peak of 13,133 cases in the week ended December 14, after which it declined to 3,030 cases for the week ended January 4. In the week ended December 21, Louisiana reported 8,000 cases. This total rose to 32,985 the following week but for the week ended January 4 declined to 7,307. On the Eastern seaboard the disease has not reached the proportions which result in reports from state authorities in New York, Massachusetts, New Hampshire, Pennsylvania and Delaware. However, New York City, which reports separately, listed 77 cases for the week ended January 4 as against 32 the week before. The present prevalence of the disease is slight in other areas of the Northeast thus far, it was stated. The National Youth Administration for New York City announced that, because of the prevalence of influenza in Maine, it was postponing the departure of two hundred and fourteen youths scheduled to leave January 7 for the Quoddy regional project at Eastport.

## Deaths in Other Countries

**Prof. Jacques Arsène d'Arsonval**, who introduced the use of high frequency current into the treatment of disease, died recently at his home near Limoges, France, the New York Times reported January 1. Born in 1851, d'Arsonval graduated in medicine at the Collège de France in Paris, with which he was associated for more than sixty years. He worked as assistant to Claude Bernard and later with Brown-Séquard, whom he succeeded as professor on the latter's death in 1897.

## Government Services

### Occupational Therapy and Recreational Aides Needed

The U. S. Civil Service Commission announces that it is accepting applications for the positions of occupational therapy aides and recreational aides. There are two grades of occupational therapy aide, full grade at \$1,800 and junior grade at \$1,620 a year. Applicants must have had fourteen units of high school study; otherwise they must pass a written general test. All applicants will be rated on their education and experience as shown in their applications and in corroborative evidence. They must not have passed their forty-fifth birthday, but this age limit does not apply to veterans granted veteran preference, up to retirement age. Applications must be on file with the commission's Washington office not later than February 10 if received from states east of Colorado and February 13 if received from Colorado and states westward. Further information may be obtained from the secretary of the Board of U. S. Civil Service Examiners at any first or second class post office or from the U. S. Civil Service Commission, Washington, D. C.

## Foreign Letters

### AUSTRALIA

(From Our Regular Correspondent)

Sept. 25, 1940.

#### New Light on Poliomyelitis

From experimental investigations carried out at the Walter and Eliza Hall Institute, Melbourne, following the epidemic of poliomyelitis in Victoria in 1937-1938, Dr. F. M. Burnet has drawn the conclusion that the virus of poliomyelitis has undergone a change. In the first place no abnormality was found in the olfactory bulbs of 10 out of 11 patients who died in the acute phase of the disease. This observation, combined with the frequency with which the virus was found in tonsils, nasopharyngeal washings and feces, points rather to other channels of invasion than to the generally accepted path of the olfactory bulbs. Changes have also been observed in the age distribution of the disease. Up to 1920 the epidemic age distribution was different from that of other acute infectious diseases. It was a disease of very young children. In several epidemics since 1920 the age incidence has altered, and it now closely resembles that of the other common infectious illnesses of childhood. Further differences between the old type of disease and that of the Victorian epidemic were noticed. Few victims escaped paralysis and there was little evidence to suggest that symptomless adults disseminated the infection. Burnet concludes that before 1920 the virus was one of low virulence but high infectivity, causing widespread and recurrent infection of both adults and children, invading the pharyngeal mucosa and only rarely revealing itself by paralysis. On the other hand, he suggests that the virus is now accommodating itself to changes in the environment and personal habits of civilized communities by becoming more definitely neurotropic and at the same time less infective and less antigenic. The widespread adult reservoir of adult infection is disappearing; thus there is less exposure of very young children, and the early school ages when random contacts increase are most affected.

#### Medical Practice in New Zealand

New Zealand celebrates this year the one hundredth anniversary of its becoming a colony of the British Empire. The dominion has acquired a system of medical practice in many respects unique, developed to meet the demand of a scattered population of just over one million people more or less remote from other medical centers. Medical training is available through the University of New Zealand, an examining body with six constituent colleges; a medical student may do his first year's work at any one of the four chief colleges, situated in Auckland, Dunedin, Christchurch and Wellington respectively. From his second to his fifth year he attends the Otago National Medical School in Dunedin, and for his sixth (clinical) year he may choose the public hospital in any one of the four cities mentioned. The number of students in each year has fluctuated between thirty and a hundred in the past twenty years. Well-to-do parents are perhaps not so much a prerequisite for medical training in New Zealand as in Europe; many students can live at home and plenty of government scholarships are available. In the early years of training, students can augment their resources by working in the country during their long vacation.

Comparatively little has been attempted in the way of original research or investigation in New Zealand, and there are few appointments for full time research work. Nor has postgraduate education been attempted. Up till twenty years ago most students went to England to qualify and there is still a strong tendency for them to go abroad after a year or two as hospital residents and before settling into practice. They usually spend from one to five years in England or America, taking resident

posts and working for a higher degree. Many, of course, never return to New Zealand but find opportunities elsewhere for special work. Those who do return usually are obliged to enter general practice, there being only a limited number of specialist appointments available. The duties falling to general practitioners in New Zealand include lodge practice (which is equivalent to panel practice), anesthetics and obstetrics. Also one may hold an appointment as senior surgeon at a public hospital and teach clinical surgery to the final year students. Owing to the great diversity of demands made on the general practitioner, the general standard of practice is probably higher than in older countries.

The public hospitals in New Zealand were founded as government institutions, in the first place to care for the Maoris, but later the poorer members of the white community made use of them. It was hoped that they would be supported by voluntary contributions and rates, but these sources proved insufficient and the government has had to assume greater responsibility for them. In 1939 under the national insurance scheme, hospital benefits were made available to all: out of a fund raised from taxation and compulsory contributions the government pays the hospital 6 shillings a day for every patient. Every citizen has a right to avail himself of the services of a public hospital, including those of the consultant staff, but private hospitals exist for those who wish to use them. Many of the well-to-do group, however, now make use of the public hospitals, and the payment offered to hospital consultants will offset the financial disadvantages they have hitherto suffered on this account.

#### Influenza Virus Infections of the Chick Embryo Lung

F. M. Burnet, working at the Walter and Eliza Hall Institute, Melbourne, has made a valuable discovery regarding the use of chick embryo in the experimental study of the viruses. In the *British Journal of Experimental Pathology* (21:147 [June] 1940) he reports that influenza virus strains can be propagated in chick embryos without preliminary adaptation when the inoculation is made through the amniotic cavity. This work is of possible importance for two reasons. First, Burnet has successfully infected chick embryo with material of human origin which has passed through only one ferret. He is optimistic that viruses obtained directly from human beings would infect equally well, though he has not yet had an opportunity to test the point. Such a rapid and reliable means of recognizing influenza virus infection in man would be of great practical value. Second, the new method offers a possible means for the isolation of some of those viruses, other than the virus of epidemic influenza, which produce respiratory disorders in man but which so far have eluded study because no susceptible test animal has been discovered. Another potentiality is the production of antigenic material from virus as little removed from the original human type as possible. In the event of a pandemic due to an antigenically new type of influenza virus, it might be of greatest value to be in a position to produce large quantities of virus.

## Marriages

THOMAS EDWARD FULGHUM to Miss Sara Martha Griffith, both of Atlanta, Ga., in Columbia, S. C., Sept. 29, 1940.

THOMAS S. BOOZER, Talladega, Ala., to Miss Sabra Thrasher of Birmingham in Montgomery, Aug. 18, 1940.

JAMES D. BILES JR., Memphis, Tenn., to Miss Elizabeth Hough Boone of Seattle, Sept. 7, 1940.

S. ROY HIGGINBOTHAM JR., Tampa, Fla., to Miss Esther E. Byrnes of Atlanta, Ga., Sept. 4, 1940.

NORTON FRIERSON JR., Atlanta, Ga., to Miss Emily Dean of Rockmart in August 1940.

HELENE N. BOYER to Mr. Temple Neiter, both of Racine, Wis., Aug. 24, 1940.

## Deaths

**Emory Hill** \* Richmond, Va.; Medical College of Virginia, Richmond, 1907; member of the House of Delegates of the American Medical Association in 1924 and from 1934 to 1936; member of the American Academy of Ophthalmology and Otolaryngology; member and formerly secretary of the American Ophthalmological Society; past president of the Virginia Society of Otolaryngology and Ophthalmology; fellow of the American College of Surgeons; instructor of ophthalmology at Rush Medical College, Chicago, from 1914 to 1919; emeritus professor of ophthalmology at his alma mater; ophthalmologist, Johnston-Willis Hospital and Tucker Sanatorium; consulting ophthalmologist, Hospital Division, Medical College of Virginia; aged 57; died, Dec. 4, 1940.

**William Robert Williams** \* New York; College of Physicians and Surgeons, medical department of Columbia College, New York, 1895; instructor of materia medica and therapeutics at his alma mater from 1906 to 1908, assistant professor of pharmacology and therapeutics from 1908 to 1914 and associate professor of clinical medicine from 1914 to 1921; instructor in medicine, Cornell University Medical College, 1903-1904, and professor of clinical medicine since 1932; aged 73; served in various capacities and at various times on the staffs of the Horton Memorial Hospital, Middletown, and St. John's Riverside Hospital, Yonkers, French Hospital, New York Infirmary for Women and Children and the New York Hospital, where he died, Nov. 17, 1940.

**Thomas Benjamin Carroll**, Pittsburgh; Jefferson Medical College of Philadelphia, 1903; member of the Medical Society of the State of Pennsylvania; member of the American Gynecological Society; fellow of the American College of Surgeons; past president of the Allegheny County Medical Society; served during the World War; aged 67; on the staff of the Woman's Hospital, St. Francis Hospital and the Montefiore Hospital, Pittsburgh, and the Columbia Hospital, Wilkesburg, where he died, Nov. 26, 1940.

**Harry Michael Stein** \* Baltimore; University of Maryland School of Medicine, Baltimore, 1914; professor of clinical medicine at his alma mater; served during the World War; aged 49; formerly superintendent of the University of Maryland Hospital, where he died, Nov. 15, 1940, of arterial hypertension, nephrosclerosis, diverticulosis of the colon and cholelithiasis.

**Samuel Lynn Wadley**, Palmer, Texas; University of Tennessee Medical Department, Nashville, 1905; member of the State Medical Association of Texas; for many years city health officer and member of the school board; past president of the Ellis County Medical Society; aged 59; died, Nov. 4, 1940, in the Dr. E. P. Becton's Hospital, Greenville, of pneumonia.

**Augustus Leon Beier**, Chippewa Falls, Wis.; Wisconsin College of Physicians and Surgeons, Milwaukee, 1907; member of the American Psychiatric Association; superintendent of the Northern Wisconsin Colony and Training School; aged 56; died, Nov. 13, 1940, in St. Mary's Hospital, Madison, of coronary thrombosis.

**Edward Isadore Steinberg** \* Eric, Pa.; Denver and Gross College of Medicine, 1907; member of the American Academy of Dermatology and Syphilology; aged 56; on the staffs of the Hamot Hospital and St. Vincent's Hospital; died, Nov. 10, 1940, of a respiratory tract infection and heart disease.

**Charles Weseley Rice** \* Northumberland, Pa.; Medico-Chirurgical College of Philadelphia, 1902; president and for many years a member of the school board; served during the World War; aged 62; on the staff of the Mary Packer Hospital, Sunbury, where he died, Nov. 24, 1940, of pneumonia.

**Isadora Sharring Powers**, Grand Rapids, Mich.; University of Michigan Homeopathic Medical School, Ann Arbor, 1894; formerly member of the board of education of Grandville; aged 79; died, Nov. 25, 1940, in the Blodgett Hospital of diverticulosis and hypostatic pneumonia.

**Charles Jefferson Woods** \* Macon, Ga.; Miami Medical College, Cincinnati, 1905; member of the American Academy of Dermatology and Syphilology; past president of the Tulsa County (Okla.) Medical Society; served during the World War; aged 60; died, Nov. 6, 1940.

**Klor Lehman Parent**, Lima, Ohio; Ohio State University College of Medicine, Columbus, 1913; member of the Ohio State Medical Association; on the staffs of the Lima Memorial Hospital and St. Rita's Hospital; aged 51; died, Nov. 20, 1940, of adenocarcinoma of the colon.

**Frederick Thompson Wright**, La Jolla, Calif.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1899; member of the Arizona State Medical Association; past president of the state board of medical examiners of Arizona; aged 75; died, Nov. 8, 1940.

**David Middleton Lawson**, Nowata, Okla.; Hospital College of Medicine, Louisville, Ky., 1899; served during the World War; for many years member of the board of education; aged 73; died, Nov. 23, 1940, of diabetes mellitus and chronic myocarditis.

**Frank Chase Wade** \* Howe, Ind.; Detroit College of Medicine, 1900; president of the Lagrange County Medical Society; for many years member of the school board; bank president; aged 63; died, Nov. 14, 1940, of arteriosclerosis with hypertension.

**Reginald P. Humphreys**, New Haven, Mich.; Wayne University College of Medicine, Detroit, 1938; member of the Michigan State Medical Society; aged 29; died, Nov. 21, 1940, in St. Joseph Hospital, Mount Clemens, of subacute bacterial endocarditis.

**Harold Dale Strausbaugh**, Columbus, Ohio; Starling-Ohio Medical College, Columbus, 1910; member of the Ohio State Medical Association; served during the World War; aged 52; died, Nov. 28, 1940, in the Mount Carmel Hospital of coronary occlusion.

**Thomas William Murphy**, Lawrence, Mass.; Tufts College Medical School, Boston, 1904; member of the Massachusetts Medical Society; aged 70; on the staff of the Lawrence General Hospital, where he died, Nov. 2, 1940, of angina pectoris.

**Hugh Parks** \* Elkin, N. C.; Jefferson Medical College of Philadelphia, 1921; aged 44; on the staff of the Hugh Chatham Memorial Hospital, where he died in November 1940 of hypertensive cardiovascular disease and coronary occlusion.

**Porter Prather**, Lexington, Ky.; Medical College of Ohio, Cincinnati, 1886; member of the Kentucky State Medical Association; aged 81; died, Nov. 28, 1940, in the Good Samaritan Hospital of a fractured pelvis received in a fall.

**Herbert Clark Waddle**, Janesville, Wis.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1903; aged 73; died, Nov. 9, 1940, in the Wisconsin General Hospital, Madison.

**John L. Stillings**, Yakima, Wash.; University of Louisville (Ky.) Medical Department, 1893; served during the World War; aged 71; died, Nov. 6, 1940, in the Veterans Administration Facility, Walla Walla.

**Benjamin Robert McGrath** \* Grand Island, Neb.; University of Illinois College of Medicine, Chicago, 1902; served during the World War; aged 67; died, Nov. 18, 1940, of cerebral thrombosis.

**Charles Elmore Trimble** \* Crestline, Ohio; Starling Medical College, Columbus, 1890; past president of the Crawford County Medical Society; aged 77; died, Nov. 26, 1940, of heart disease.

**Frank Guillard**, Saxton, Pa.; Medico-Chirurgical College of Philadelphia, 1914; served during the World War; aged 50; died, Nov. 19, 1940, in the J. C. Blair Memorial Hospital, Huntingdon.

**Frederick William Veninga** \* St. Louis; American Medical College, St. Louis, 1906; aged 66; on the staff of the Lutheran Hospital, where he died, Nov. 10, 1940, of chronic myocarditis.

**Charles Materazzi**, Paterson, N. J.; Regia Università di Napoli Facoltà di Medicina e Chirurgia, Italy, 1911; aged 54; died, Nov. 14, 1940, in Perdisumo, Cilento, Italy, of influenza.

**Thomas Ellsworth Schrider**, Bryan, Ohio; Long Island College Hospital, Brooklyn, 1889; aged 78; died, Nov. 23, 1940, in St. Vincent's Hospital, Toledo, of obstructive jaundice.

**William Henry H. Barker**, Harvey, Iowa; Harvey Medical College, Chicago, 1898; Civil War veteran; also a dentist; aged 100; died, Nov. 8, 1940, of chronic myocarditis.

**Ronald Robertson Smith**, Tulsa, Okla.; University of Kansas School of Medicine, Kansas City, 1906; aged 56; was found dead in bed in November 1940 of heart disease.

**Adolph Otto Sistler** \* Hoopeston, Ill.; University of Louisville (Ky.) Medical Department, 1910; aged 57; died in November 1940 of myocarditis.

**Frank Renel Lord**, Covington, Ky.; Miami Medical College, Cincinnati, 1894; aged 68; died, Nov. 26, 1940, of cerebral edema.

## Bureau of Investigation

### MISBRANDED "PATENT MEDICINES"

#### Abstracts of Notices of Judgment Issued by the Food and Drug Administration of the United States Department of Agriculture

[EDITORIAL NOTE.—The abstracts that follow are given in the briefest possible form: (1) the name of the product; (2) the name of the manufacturer, shipper or consigner; (3) the composition; (4) the type of nostrum; (5) the reason for the charge of misbranding and (6) the date of issuance of the Notice of Judgment—which is considerably later than the date of the seizure of the product and somewhat later than the conclusion of the case by the Food and Drug Administration.]

**Acid Eliminating Powder.**—Ray Alma Richardson, Helen Richardson (Mrs. R. A. Richardson) and Myra Deane Richardson, trading as the Myra Deane Co., Kansas City, Mo. Composition: essentially baking soda, sodium carbonate, chalk, magnesium oxide and peppermint. Misbranded because of its misleading name, since the article was not an acid eliminant as so understood; misbranded further because fraudulently represented to eliminate indigestion, avert or correct active or passive liver congestion, prevent abscess or cirrhosis of the liver, remedy female weaknesses, sexual frigidity, hay fever or asthma, correct constipation, hives, acidosis or skin eruptions, and prevent rheumatism, arthritis, mental depression or congestion of the heart and gallbladder.—[N. J. 30964; August 1940.]

**Agalax.**—Associated Laboratories, Inc., and the Agalax Company, New York. Composition: essentially psyllium seed and small brown masses containing sugar, starch, dextrin and phenolphthalein (0.13 grain per teaspoonful). Misbranded because represented to be a food and to contain no drug or medicine, whereas it did contain phenolphthalein, a coal tar drug; further misbranded because fraudulently represented as a cure for chronic constipation, autointoxication and allied conditions, and as a relief for hemorrhoids and painful defecation.—[N. J. 30960; August 1940.]

**Chippewa Genuine Guaranteed Old Indian Medicine.**—Lucky Heart Laboratories, Inc., Memphis, Tenn. Composition: essentially epsom salt, plant drugs including a laxative (licorice) and water colored with caramel. Falsely represented to consist entirely of substances from roots, herbs and berries. Fraudulently represented to be effective as a general tonic and as a cure for tired feeling, nervousness and indigestion, sour stomach, torpid liver, impure blood and some other things.—[N. J. 30965; August 1940.]

**Chippewa Indian Herbs Tea.**—Lucky Heart Laboratories, Inc., Memphis, Tenn. Composition: essentially plant material including juniper berries, fennel seed, licorice root, anise seed, unidentified flower petals and a woody material. For upset stomach, biliousness, headaches, bad complexion, rundown health, dyspepsia, impure blood and liver and kidney disorders. Fraudulent therapeutic claims.—[N. J. 30965; August 1940.]

**Glaassen Health Yeast.**—National Yeast Co., Inc., Findlay, Ohio. Composition: less than 2 International Units of vitamin B<sub>1</sub>, not more than 50 U. S. P. units of vitamin A and approximately 10 U. S. P. units of vitamin D per gram; also ground corn and corn starch, wheat tissues (bran), embryo tissues (germ) apparently from cereals, yeast cells, crystalline dextrose hydrate (corn sugar), crystalline sucrose (sugar) and a trace of hop tissues. Fraudulently represented as a health yeast conducive to a clear skin; as a cure for indigestion, acid stomach, bad breath, hemorrhoids, skin blemishes, diarrhea, stunted growth, loss of weight and appetite, anemia, diabetes, tuberculosis and some other things; contained ingredients other than yeast and was not so represented.—[N. J. 30975; August 1940.]

**Coal Breaker Pills.**—Lucky Heart Laboratories, Inc., Memphis, Tenn. Composition: acetanilid (0.93 grain per pill), extracts of plant drugs including capsicum and a laxative, small proportions of camphor, a quinine and an iron compound, chalk and talc. For biliousness, dizziness, sour stomach, gas, colic and "infection." Misbranded because of fraudulent therapeutic claims and label statement "Contains bromides," whereas government chemists reported finding none; further misbranded in containing acetanilid not declared on the label.—[N. J. 30965; August 1940.]

**Erbru Pine Compound Cough Syrup.**—Lucky Heart Laboratories, Inc., Memphis, Tenn. Composition: essentially extracts of plant drugs, including white pine, with chloroform (6 minims per fluid ounce), sugar and water, colored with caramel. Misbranded because presence and amount of chloroform not declared on label.—[N. J. 30965; August 1940.]

**Formula No. DP 64 Duodenin and Pancreas Substance Tablets.**—Ray Alma Richardson, Helen Richardson (Mrs. R. A. Richardson) and Myra Deane Richardson, trading as the Myra Deane Co., Kansas City, Mo. Composition: considerable amount of animal tissues, apparently glandular in nature, and crystalline milk sugar. Misbranded because label statement "Contains Duodenin and Pancreas Substance" falsely represented that the product contained duodenin and pancreas and was active and effective because these substances were present, whereas the product consisted of inert animal material resembling glandular substance, and milk sugar; further misbranded because the claim "Useful in Diabetes Mellitus" fraudulently represented the article as being medically effective in treating that condition, which it was not.—[N. J. 30964; August 1940.]

**Formula No. FH 60 Endocrine Compound Female.**—Ray Alma Richardson, Helen Richardson (Mrs. R. A. Richardson) and Myra Deane Richardson, trading as the Myra Deane Co., Kansas City, Mo. Composition: compressed tablets composed essentially of milk sugar and animal protein matter resembling glandular substances. Misbranded because

feeding tests on animals showed the product inert in doses of one or two tablets per animal; further misbranded because fraudulently represented as a remedy for organs whose functions are related to and affect the female menstrual cycle.—[N. J. 30964; August 1940.]

**Formula No. FH 60 Endocrine Cycle Food Female.**—Ray Alma Richardson, Helen Richardson (Mrs. R. A. Richardson) and Myra Deane Richardson, trading as the Myra Deane Co., Kansas City, Mo. Composition: compressed tablets composed essentially of milk sugar and animal protein matter resembling glandular substances. Misbranded because statements on label "Contains interrelated gland substances of the female endocrine cycle" and "Endocrine Cycle Food Female" falsely represented that the ingredients were active gland substances and that the product was capable of producing an enzymic action, whereas it consisted of inert animal matter resembling glandular substance and milk sugar and could not produce enzymic action; further misbranded because fraudulently represented as a remedy for organs whose functions are related to and affect the feminine menstrual cycle; and as being effective in restoring health, vitality or "pep," correcting overweight or underweight, toxic goiter, fibroid tumor and some other things.—[N. J. 30964; August 1940.]

**Formula No. HBP 98 For Controlling High Blood Pressure.**—Ray Alma Richardson, Helen Richardson (Mrs. R. A. Richardson) and Myra Deane Richardson, trading as the Myra Deane Co., Kansas City, Mo. Composition: compressed tablets essentially containing glandular material including 0.09 Gm. of thyroid per tablet. Misbranded because falsely labeled "No Drugs," whereas it contained thyroid and other glandular material; further misbranded because the statements "for controlling high blood pressure" and "contains pancreas and thyroid substances in balanced combination to aid in controlling high blood pressure" were false and fraudulent, since the product was inert.—[N. J. 30964; August 1940.]

**Formula No. RS 63.**—Ray Alma Richardson, Helen Richardson (Mrs. R. A. Richardson) and Myra Deane Richardson, trading as the Myra Deane Co., Kansas City, Mo. Composition: a considerable amount of animal tissues, apparently glandular in nature, and crystalline milk sugar with finely ground bone. Misbranded because falsely labeled "Rich in calcium salts and iron," whereas each tablet contained not more than 0.28 grain (0.018 gram) of combined calcium and not more than 0.0027 grain (0.00017 gram) of combined iron; further misbranded because falsely and fraudulently represented as being effective in the treatment of secondary anemia, whereas it was not.—[N. J. 30964; August 1940.]

**Hain Col-Lax.**—Hain Pure Food Co., Los Angeles. Composition: ground psyllium, agar and milk sugar. Fraudulently represented as a noncaustic safe to use in colitis, ulceration and hemorrhoids.—[N. J. 30954; August 1940.]

**Hain Kelp Tablets.**—Hain Pure Food Co., Los Angeles. Composition: powdered kelp. Fraudulently represented as a cure for glandular deficiencies, nervous debility, mental exhaustion and general rundown conditions.—[N. J. 30954; August 1940.]

**Oralsulin.**—Lafayette Pharmacal, Inc., Lafayette, Ind. Composition: essentially powdered animal tissues, including a small amount of an enzyme such as found in pancreas tissue; one sample contained starch and another powdered ginger. Biologic tests showed no evidence of insulin activity following oral administration. Adulterated because far below strength and purity of professed standard and quality and because falsely represented to consist of "Enterocap Oralsulin," namely, insulin or similar substance intended for oral administration. Misbranded because represented on label to be an oral substitute for insulin injections and fraudulently represented as an effective treatment for diabetes mellitus.—[N. J. 30998; August 1940.]

**Orone Hygiene Soap.**—Lucky Heart Laboratories, Inc., Memphis, Tenn. Composition: a sodium soap, colored and perfumed. Recommended for use in connection with "Heal-O-Solve" to relieve discomfort and varieties of open sores, irritated skin and similar disorders. Fraudulent therapeutic claims including that of "antiseptic."—[N. J. 30965; August 1940.]

**Pinip.**—Merit Laboratories Co., Philadelphia. Composition: not given. Adulterated because it approximately contained only 250 U. S. P. units of vitamin D instead of the 1,000 units claimed on the label.—[N. J. 30963; August 1940.]

**Pinip Laxative Cold Capsules.**—Merit Laboratories, Philadelphia. Composition: one specimen, a minimum of 3.03 grains of acetophenetidin, 1.30 grains of acetanilid and about 20 units of vitamin C. Misbranded because the presence and amount of acetophenetidin, a derivative of acetanilid, were not declared on the label; further misbranded because the label falsely declared that the acetanilid content of each capsule was only 1 grain, whereas it was not less than 1.3 grains; misbranded further because fraudulently represented to lessen the acidity of the body and facilitate the absorption of the active vitamin principles of citrus fruits.—[N. J. 30963; August 1940.]

**Saurinol.**—Saurinol Distributors, Colorado Springs, Colo. Composition: medium boiling petroleum oil with a small proportion of quinine alkaloid. Fraudulently represented as a cure for exposed cancer, pyorrhea, varicose veins, trench mouth, sinus trouble, hay fever, lacerations, ulcers and skin diseases.—[N. J. 30953; August 1940.] The Saurinol business was declared fraudulent and debarred from the mails in February 1940 as reported in THE JOURNAL, Sept. 21, 1940, page 1037.

**Snare's Re-Lef.**—Snare Bros. Ointment Co., Chillicothe, Mo. Composition: essentially volatile oils including mustard, wintergreen, menthol and a camphoraceous one, in a petrolatum base. Fraudulently represented as a cure for pneumonia and an effective treatment for sinus trouble, asthma, rheumatism, hemorrhoids, appendicitis, open sores, pleurisy and some other things.—[N. J. 30957; August 1940.]

**X-ODE.**—X-Products Co., St. Paul. Composition: sodium carbonate (99.15 per cent) and potassium permanganate (0.85 per cent). Falsely and fraudulently represented as efficacious for treating skin infections.—[N. J. 30959; August 1940.]



## Correspondence

### LECTURES ON MEDICAL ECONOMICS

*To the Editor:*—In connection with your editorial comment on "Teaching of Social Medicine" in THE JOURNAL, Dec. 7, 1940, page 2001, it may interest you to know that in each of the last three years the speakers' bureau of the Committee on Public Relations of the Philadelphia County Medical Society has furnished six lecturers on socialized medicine for the classes in economics in the various schools of the University of Pennsylvania.

MYER SOLIS-COHEN, M.D., Philadelphia.

Chairman, Committee on Public Relations.

### MEDICAL DICTION AND TERMINOLOGY

*To the Editor:*—Twice today I have had telephone calls, from independent sources, stating that "a complete g-i examination" was desired. On cross examination—which should not be necessary but which I can testify is—it was revealed that an examination of only the stomach was desired.

How much wasted effort and often expense would be saved if physicians could get together on terminology! To a roentgenologist g means gastro and i means intestinal, and any referring physician who gets on a high horse to my secretary when she tries to find out whether "a complete g-i examination" means a stomach and colon, a stomach and small intestine and colon or only a stomach is in a vulnerable position, as people always are who ride on high horses. If the terminology used by many physicians of my acquaintance reflects their schoolday teaching, the teaching has been sloppy.

Another thing that annoys me is for physicians to request a "g-u examination." G stands for genital and u for urinary, at least to me, and there is seldom any occasion to examine a man's genital apparatus when the point at issue is a stone in his urinary apparatus. In fact, I have gone to considerable pains to try to educate some of the profession that any irradiation of the germ plasma of any person who is not past the reproductive period—and who can say, in the case of a male, when a patient is past any possibility of reproducing his kind?—is fraught with dire consequences to future generations unless the human germ plasma reacts differently from the germ plasma of the twenty-nine genera of other animals that have been studied to date.

Another daily request that reflects a total lack of comprehension of semantics is to ask for a "flat plate." A plate is made of glass, and I never saw one yet devoted to roentgenographic purposes that was not flat. Glass plates went out not long after bustles did; today films are used, and they are just as flat as glass plates ever were, unless one wants to lay emphasis on the curved cassette that had a vogue a few years ago; even the product of this gadget was flat when it was put up for inspection. To ask for a flat plate when a film is meant, or even to ask for a flat film, is like asking for an egg omelet. I think that what is meant is a single film as opposed to a stereoscopic pair; at least the context practically always leads to that conclusion. It doesn't mean that it is desired to have the patient flat on the table, because I am frequently asked for a "flat plate upright" when the question is the determination of the presence of air under the right diaphragm in a case of suspected perforated ulcer.

As I get older, I look back with even more sympathy than I had at the time on my erstwhile professor of surgery Charles L. Gibson, who invariably interrupted the student who mentioned "lymph glands" with "please don't say lymph glands in my clinic," and would explain that glands are epithelial structures with a secretion, which lymph nodes quite definitely are not. One can search the whole world over but will never

find a Cornell graduate of Gibson's time who will say "lymph glands." However, the misuse of the term is so well nigh universal that if a man says "lymph nodes" one can bet with reasonable safety that he was once a student of Gibson's.

To go out of my own field, which I was never averse to do, I should like to pay my respects to the persons who can spare no longer designation for the wares of the string galvanometer than "E. K. G." To ask for an elektrokardiogramm by the initials of its component German words is to pay homage to a language which at the moment is not identified with scientific freedom. If Einthoven could go to the trouble to invent the string galvanometer, I think people should go to the trouble to pronounce "electrocardiogram." I'm not saying that I think they will; I'm just saying that I think they should.

The late Dr. E. W. Caldwell used to say that roentgenology would be an enjoyable occupation if it weren't for the patients. I will modify that to say that roentgenology wouldn't be so bad if physicians would only tell the roentgenologist what they mean. There used to be a song upward of thirty years ago—if I recall correctly, it was in a show of Raymond Hitchcock's—that went

If people said the things they mean  
And meant the things they say.

It's still good.

RAMSAY SPILLMAN, M.D., New York.

### AN ACUTE PUBLIC HEALTH PROBLEM OF IMMIGRATION

*To the Editor:*—Even in normal times, port cities are confronted with health problems of unique character. San Francisco always has had certain definite health problems with regard to travelers coming from the Orient. Recently, however, a new angle has developed. Early in 1940 roentgen examinations of the positive reactors to tuberculin in the routine testing done in San Francisco schools showed an unusually large number of Chinese boys in junior high school with far advanced clinical tuberculosis.

For a period of ten years past, high school and junior high school students in this city have received tuberculin tests every year. The tests done are an intracutaneous Mantoux of 1:1,000 dilution. Roentgenograms of the positive reactors are made and the negative reactors are retested at regular intervals throughout their school life. The incidence of clinical tuberculosis and the mortality are considerably higher in the Chinese population than for the rest of the city.

During the first three months of 1940, 26 Chinese children were removed from school because of clinically active tuberculosis. They all had far advanced tuberculosis; one had bilateral cavitation and none of the cases looked recent. Twelve additional patients are under observation. Many were found to have spent varying lengths of time in China. Of the 26, 5 were girls and 21 were boys or, rather, young men, since they are all much older than the usual junior high school age. The 12 under observation are all boys. The ages of these students is an important factor. These ranged between 16 and 23 years; the average junior high school age in San Francisco is 12 or 13 years.

An investigation revealed that many of these boys had been recently admitted to the United States as American citizens or as children of American citizens without any kind of a physical examination. All had been visitors to a district in or near Canton, China, where their time of residence varied from life to ten years. The length of time after return to the United States varied from four months to two years. It is evident that there has been in 1940 in San Francisco a decided increase in the number of clinically active cases of tuberculosis among Chinese boys of the junior high school grades.

Investigation has shown that Chinese have taken their sons with them to China. The boys have lived in the vicinity of

Canton, China, under adverse public health conditions not found in the United States, and more recently under actual war conditions. Whenever possible, Chinese have returned their sons to the safety of the United States. The boys are American citizens who are classified merely as having been away on a vacation, or in other cases they are the children of American born Chinese born in China. In this situation lies a menace of tuberculosis, especially to the Chinese population of San Francisco. It would seem desirable to have a roentgenogram of the chest of all young Chinese returning to the United States after a prolonged sojourn in China.

This is merely one age and one race group. The cost to San Francisco in three months alone for the care of these Chinese youths with active tuberculosis and the probable necessity of shortly caring for additional cases would justify taking every precaution at the port of debarkation by proper federal authorities in order to limit further the spread of tuberculosis in the United States.

J. C. GEIGER, M.D.

ETHEL OWEN, M.D.

Department of Public Health, San Francisco.

## Medical Examinations and Licensure

### COMING EXAMINATIONS

#### BOARDS OF MEDICAL EXAMINERS

ALABAMA: Montgomery, June 17-19. Sec., Dr. J. N. Baker, 519 Dexter Ave., Montgomery.

ARKANSAS: \* *Medical*. Little Rock, June 5-6. Sec., Dr. D. L. Owens, Harrison. *Eclectic*. Little Rock, June 5-6. Sec., Dr. Clarence H. Young, 1415 Main St., Little Rock.

CALIFORNIA: *Oral examination* (required when reciprocity application is based on a state certificate or license issued ten or more years before filing application in California), Los Angeles, Jan. 29. *Written*. Los Angeles, Feb. 24-27. Sec., Dr. Charles B. Pinkham, 1020 N St., Sacramento.

CONNECTICUT: \* *Medical*. *Written*. Hartford, March 11-12. *Endorsement*. Hartford, March 25. Sec., Dr. Thomas P. Murdock, 147 W. Main St., Meriden. *Homeopathic*. Derby, March 11-12. Sec., Dr. Joseph H. Evans, 1488 Chapel St., New Haven.

DELAWARE: July 8-10. Sec., Medical Council of Delaware, Dr. Joseph S. McDaniel, 229 S. State St., Dover.

DISTRICT OF COLUMBIA: \* Washington, May 12-13. Sec., Commission on Licensure, Dr. George C. Ruhland, 203 District Bldg., Washington.

FLORIDA: \* Jacksonville, June 23-24. Sec., Dr. William M. Rowlett, Box 786, Tampa.

GEORGIA: Atlanta, June. Sec., State Examining Boards, Mr. R. C. Coleman, 111 State Capitol, Atlanta.

IDAHO: Boise, April 1. Dir., Bureau of Occupational License, Mr. H. B. Whittlesey, 335 State Capitol Bldg., Boise.

ILLINOIS: *Written*. Chicago, Jan. 21-22. *Reciprocity*. Chicago, Jan. 23. Supt. of Registration, Dept. of Registration and Education, Mr. Lucien A. File, Springfield.

INDIANA: Indianapolis, June 17-19. Sec., Board of Medical Registration and Examination, Dr. J. W. Bowers, Citizens Trust Bldg., Fort Wayne.

KANSAS: Kansas City, June 17-18. Sec., Board of Medical Registration and Examination, Dr. J. F. Hassig, 905 N. 7th St., Kansas City.

MAINE: Portland, March 11-12. Sec., Board of Registration of Medicine, Dr. Adam F. Leighton, 192 State St., Portland.

MARYLAND: *Medical*. Baltimore, June 17-20. Sec., Dr. John T. O'Mara, 1215 Cathedral St., Baltimore.

MASSACHUSETTS: Boston, March 11-13. Sec., Board of Registration in Medicine, Dr. Stephen Rushmore, 413-F S.

MICHIGAN: \* Ann Arbor and Detroit, June 14-15. Sec., Board of Registration in Medicine, Dr. J. Earl M.

MINNESOTA: \* Minneapolis, Jan. 21-23. Sec., Dr. Julian F. Du Bois, 350 St. Peter St., St. Paul.

MISSISSIPPI: Jackson, June. Asst. Sec., State Board of Health, Dr. R. N. Whitfield, Jackson.

MONTANA: *Reciprocity*. Helena, March 31. *Written*. Helena, April 1. Sec., Dr. S. A. Cooney, 216 Power Block, Helena.

NEVADA: *Reciprocity with oral examination*, Feb. 3. Sec., Dr. Fred M. Anderson, 215 N. Carson St., Carson City.

NEW HAMPSHIRE: Concord, March 13-14. Sec., Board of Registration in Medicine, Dr. T. P. Burroughs, State House, Concord.

NEW JERSEY: Trenton, June 17-18. Sec., Dr. Earl S. Hallinger, 28 W. State St., Trenton.

NEW MEXICO: Santa Fe, April 14-15. Sec., Dr. Le Grand Ward, 135 Sena Plaza, Santa Fe.

NEW YORK: Albany, Buffalo, New York and Syracuse, Jan. 27-30. Chief, Bureau of Professional Examinations, Mr. Herbert J. Hamilton, State Education Department, 315 Education Bldg., Albany.

SOUTH DAKOTA: \* Pierre, Jan. 21-22. Dir., Medical Licensure, Dr. J. F. D. Cook, Pierre.

VERMONT: Burlington, Feb. 11. Sec., Dr. W. Scott Nay, Underhill.

WEST VIRGINIA: Charleston, March 3. Sec., Public Health Council, Dr. Arthur E. McClue, State Capitol, Charleston.

WYOMING: Cheyenne, Feb. 3-4. Sec., Dr. M. C. Keith, Capitol Bldg., Cheyenne.

\* Basic Science Certificate required.

### BOARDS OF EXAMINERS IN THE BASIC SCIENCES

ARIZONA: Tucson, March 18. Sec., Mr. Franklin E. Roach, Science Hall, University of Arizona, Tucson.

COLORADO: March 6-7. Sec., Dr. Esther B. Starks, 1459 Ogden St., Denver.

CONNECTICUT: Feb. 8. Address State Board of Healing Arts, 150 Yale Station, New Haven.

DISTRICT OF COLUMBIA: Washington, April 21-22. Sec., Commission on Licensure, Dr. George C. Ruhland, 203 District Bldg., Washington.

FLORIDA: De Land, June 7. *Applications must be on file not later than May 24*. Sec., Prof. J. F. Conn, John B. Stetson University, De Land.

MICHIGAN: Ann Arbor, Detroit and East Lansing, Feb. 14-15. Sec., Miss Flora E. Dube, East Lansing.

OREGON: Portland, Feb. 15. Sec., State Board of Higher Education, Mr. Charles D. Byrne, University of Oregon, Eugene.

RHODE ISLAND: Providence, Feb. 19. Sec., Division of Examiners, Rev. Nicholas H. Serror, Providence College, Providence.

WISCONSIN: Madison, April 5. Sec., Prof. Robert N. Bauer, 344 W. Wisconsin Avenue, Milwaukee.

### Colorado October Report

Dr. Harvey W. Snyder, secretary, Colorado State Board of Medical Examiners, reports the written examination for medical licensure held at Denver, Oct. 2-4, 1940. The examination covered 8 subjects and included 69 questions. An average of 75 per cent was required to pass. Seven candidates were examined, 6 of whom passed and 1 failed. Two physicians were licensed to practice medicine by reciprocity and 1 physician so licensed by endorsement. The following schools were represented:

School	PASSED	Year Grad.	Per Cent
University of Colorado School of Medicine.....	(1938)		84.5
University of Chicago, The School of Medicine.....	(1940)		85
Tulane University of Louisiana School of Medicine.....	(1940)		86.5
Harvard Medical School.....	(1939)		84
Osteopaths *		80, 80	

School	FAILED	Year Grad.	Number Failed
Osteopaths *			1

School	LICENSED BY RECIPROCITY	Year Grad.	Reciprocity with
Northwestern University Medical School.....	(1939)		Illinois
University of Oklahoma School of Medicine.....	(1935)		Oklahoma

School	LICENSED BY ENDORSEMENT	Year Endorsement Grad.	of
College of Medical Evangelists.....	(1940)	N. B. M. Ex.	

\* Examined in medicine and surgery.

## Miscellany

### CHILD HEALTH AND MATERNAL CARE

#### Report and Recommendations of Subcommittees Submitted to Maternal and Child Health Advisory Committee Meeting at the Children's Bureau, Adopted by the Full Committee

The following reports were submitted to the Children's Bureau Maternal and Child Health Advisory Committee by the subcommittees on child health and maternal care and, after discussion, were adopted unanimously on December 3 by the full committee:

#### REPORT OF THE SUBCOMMITTEE ON CHILD HEALTH

The national defense program has caused a rapid increase in population in villages, towns and cities adjacent to military cantonnments and in those with rapidly expanding defense industries. Such expansion of population brings with it urgent problems of health protection for the whole populace, but especially for children and pregnant women in the families of workers and enlisted men.

The committee recognizes that these concentrations of population have come about for purposes related to the whole of the population of the United States, not merely the areas in which they occur. The problems arising from them are the concern of the whole of the United States, and the failure to meet them is a potential adverse influence on the whole country.

In view of this emergency, the advisory subcommittee on child health of the Children's Bureau has given careful consideration to the urgency of providing facilities to meet existing conditions—bad housing, crowding of households, inadequate provision for recreation, bad sanitary facilities, inadequate control of communicable diseases, and lack of health supervision and medical care for mothers and children.

The committee recognizes the progress that has been made under the maternal and child health program in establishing state and local services for mothers and children. There must be no interruption in the development of this long-range program. The committee is also cognizant of the fact that large gaps in this program still exist which must be closed if anything approaching an adequate program is to be put into effect.

Because of the greatly intensified and additional problems created by national defense, however, the need for immediate expansion of these services is even more urgent than was previously apparent. The experience gained in the last few years has made it possible to outline clearly the ways in which this emergency may be met. Two obstacles present themselves, however: lack of funds and deficiency of trained personnel.

The advisory subcommittee on child health therefore recommends:

1. That increased resources be made available to the Children's Bureau to enable it—

(a) to hasten the development of an adequate maternal and child health program commensurate with existing needs for health services and medical care through substantially increased grants-in-aid to states under title V of the Social Security Act;

(b) to make careful investigations of the health, medical, housing and recreation facilities available to wives and children of workers living in or near the defense industry areas and of enlisted men in communities near military cantonments, and to provide facilities and services to meet the health and medical needs as they are found to exist; and

(c) to plan for the protection of mothers and children in any other emergency situation arising from national defense. We refer here to the immediate making of appropriate plans for the protection of mothers and children in areas of military danger and for their evacuation and placement in selected reception areas.

2. That, in view of the known insufficiency of personnel for the care of mothers and children, the Selective Service Board, the local draft boards and the military services be urgently requested, in calling physicians for military duty, to give as much consideration as possible to retaining in the local communities those physicians who are responsible, in the fields of public health and medical practice, for maternal and child care.

The advisory subcommittee on child health further recommends:

1. That, in view of the necessity for recognition by the National Defense Council of the needs of mothers and children in the civilian population, the Children's Bureau be given representation in the Health and Medical Committee of the National Defense Council;

2. That the resolution of the Academy of Pediatrics calling for the appointment of a pediatrician to the Health and Medical Committee be endorsed; and

3. That the chairman of the Maternal and Child Health Advisory Committee transmit these recommendations to the Secretary of Labor and seek an appointment with the President of the United States to lay before him the recommendations of the committee and to discuss the urgent need to safeguard the health and welfare of mothers and children as part of the national defense program.

#### REPORT OF THE SUBCOMMITTEE ON MATERNAL CARE

The committee recognizes that the great improvement in maternal and infant care which has resulted from the leadership and efforts of the medical profession are not uniform throughout the country. It is our belief that in many areas of the United States, especially where maternal and infant death rates are highest, there is urgent need for providing medical and hospital care for maternity patients and newborn infants who cannot now obtain this care. New and urgent situations have been and are being created by the concentration of families in areas where defense programs are being developed. Plans must be made immediately to provide the mothers and children in these areas with needed health services.

It is recognized that the need for better maternal and child care is intimately connected with other economic and medical deficiencies and that a truly effective program must have broad objectives and must be developed in cooperation with other governmental agencies.

In the opinion of the committee the problem of medical and hospital care for mothers and infants in many of the areas of greatest need would be solved by extending the use of existing facilities and by constructing and maintaining new hospitals where needed for the care of maternity patients and newborn infants with adequate safeguards to protect the quality of service in these institutions.

The committee recommends that additional funds be appropriated under title V of the Social Security Act to assist the state and local health agencies in meeting the health needs of mothers and children, both by extending the use of existing facilities and by establishing and maintaining hospitals for the care of mothers and newborn infants where needed.

Since the evacuation of mothers and infants from densely populated areas is an ultimate possibility, it is further recommended that plans be considered for transporting such persons to safe areas and for providing the medical and hospital services which may be needed.

## Bureau of Legal Medicine and Legislation

### MEDICOLEGAL ABSTRACTS

**Osteopathy: Right of Practitioner to Practice Optometry.**—Mabry, who was not licensed to practice medicine, optometry or any other form of the healing art, sold eyeglasses or spectacles in Atlanta, Ga., purportedly as a dispensing optician. He employed on a full time salary basis Turner, who possessed only a license to practice osteopathy in Georgia. Turner examined the eyes of such persons as were sent to him by Mabry or might otherwise come to him and, if the examinations indicated the necessity for eyeglasses, wrote prescriptions for lenses to be filled by Mabry. Mabry in turn took measurements to ascertain the necessary width of the frame and the size of the glasses and had the lenses ground according to Turner's prescription by a New York manufacturer, which also made the frames. The manufacturer sent the eyeglasses to Mabry, Turner checked the lenses against the prescription and delivered the glasses to the patient. The price that the patient paid to Mabry embraced the cost of the materials and a charge for the examination and prescription. The Georgia state board of examiners in optometry and its individual members, alleging that the acts of Mabry and Turner constituted the practice of optometry, that neither of them was licensed or otherwise entitled so to practice and that their acts constituted a menace and nuisance dangerous to the public health and safety, filed a bill to restrain Mabry and Turner from carrying on the activities referred to. The trial court issued a temporary injunction and Mabry and Turner appealed to the Supreme Court of Georgia.

Apparently the appellants assumed that the legality of the activities of both of them turned on whether or not Turner by virtue of his license to practice osteopathy could practice optometry. They contended that Turner could legally practice optometry without obtaining a license under the Georgia optometry practice act because (1) the optometry act, by its very terms, was not applicable to a licensed osteopath, a section of the act (Ga. Code, Sec. 84-1108) specifically providing that "Nothing in this Chapter shall be construed to apply to physicians and surgeons duly licensed to practice medicine," and (2) the Georgia osteopathic practice act authorizes its licentiates to practice osteopathy "as taught and practiced in legally incorporated and reputable colleges of osteopathy" (Sec. 84-1209) and Turner in the osteopathic school which he attended was taught "ophthalmology, which includes measurement of power of vision and adaptation of lenses to correct faulty or defective sight."

The appellants' first contention, said the Supreme Court, that Turner is exempted from the provisions of the optometry act because it exempts physicians and surgeons duly licensed to practice medicine, turns on whether or not Turner is, within the meaning of that act, a physician and surgeon duly licensed to practice medicine. The osteopathic practice act, under which Turner was licensed, authorizes its licentiates to practice osteopathy "as taught and practiced in legally incorporated and reputable colleges of osteopathy." Unfortunately for the courts, in enacting the osteopathic practice act in 1909, the legislature did not define "osteopathy" but left the meaning to be determined by how osteopathy was taught and practiced in reputable colleges of osteopathy. In construing a similar statute in Kansas, the tenth circuit court of appeals, in *Burke v. Kansas State Osteopathic Association*, 111 F. (2d) 250, 256, reached the conclusion that

the fact that in an osteopathic college the broad principles of medicine and surgery were investigated and considered, merely for the purpose of giving the student body a knowledge of what those who practice medicine and surgery believe, would not be sufficient to conclude that those licensed to practice osteopathy would have the right to practice medicine or surgery.

In construing an exception in the New Jersey optometry practice act similar to that contained in the Georgia act, the supreme court of New Jersey in *State v. Walters*, 143 A. 749, held that a licensed osteopath cannot practice optometry because he is

not in the category of a licensed physician who may practice medicine and surgery. The term osteopathy, the Georgia court continued, is defined in 46 C. J. 1142 as follows:

A modern system or science of treating human diseases by kneading and rubbing the body; a method of treating diseases of the human body without the use of drugs, by means of manipulations applied to various nerve centers, chiefly those along the spine, with a view to inducing free circulation of blood and lymph, and an equal distribution of the nerve forces.

Bouvier's Law Dictionary (Student's Ed., p. 881) defines osteopathy as

a method of treating diseases by kneading or manipulation of the body, and does not teach surgery, bacteriology, materia medica, or therapeutics.

The term is likewise defined by Webster's New International Dictionary as

A system of treatment based on the theory that diseases are chiefly due to deranged mechanism of the bones, nerves, blood vessels, and other tissues, and can be remedied by manipulations of these parts.

From these definitions, said the court, it is apparent that "osteopathy is based on the theory that human ailments result from disarrangement or misplacement of bones, nerves, and blood vessels, and that the cure for the ailment is the correction of such misplacement, thereby giving nature an opportunity to heal." It follows that in a reputable college of osteopathy, as referred to by the Georgia statute, the course of study taught and practiced must conform to these authoritative definitions. Any course taught or practiced which is outside the true scope of osteopathy cannot be brought within its scope merely because it is given by an osteopathic college. The Georgia osteopathic practice act, properly construed, authorizes the licensee thereunder to practice osteopathy, and that only as taught by reputable colleges.

We now turn, continued the court, to a consideration of the language "physicians and surgeons duly licensed to practice medicine." A license to practice medicine can be issued in Georgia only by the state board of medical examiners. Consequently a license issued by the osteopathic board, regardless of what such license purports to authorize, does not and cannot authorize the "practice of medicine" as that term is defined in the only statute in this state defining the practice of medicine, the medical practice act. A provision in the medical practice act, declaring that nothing therein shall be construed to prohibit "the practice of . . . osteopaths not prescribing medicines or administering drugs" (Ga. Code, Sec. 84-906), permits an osteopath to practice osteopathy without procuring a license to practice medicine, provided he does not prescribe medicine or administer drugs. This exemption, however, does not enable an osteopath to prescribe medicine, whether that medicine be a drug or otherwise; and at this point the question arises whether lenses for the relief of eye trouble should be classified as medicine. In the present case, defendant Turner made a practice of issuing prescriptions for lenses. Certainly the exemption in the medical practice act just referred to constitutes no authority for such practice. It was obvious to the court that Turner did not qualify under the medical practice act as a "physician and surgeon duly licensed to practice medicine."

The court could not agree with the appellants' contention that certain statutory provisions of the Georgia Code (Sec. 84-9918 and Sec. 84-9919), which in prohibiting the fraudulent practice of osteopathy employs the language "osteopathy, or other nondrug-giving school of medical practice," indicated a legislative intention to classify the practice of osteopathy as medical practice. Granting, said the court, that osteopathy is a nondrug-giving medical practice, a license so to practice cannot be a substitute for a license to practice medicine issued under the medical practice act. The positive requirements of the medical practice act cannot be evaded or nullified by the language used in a negative sense and for an entirely different purpose in the sections pointed out by the appellants. In the judgment of the court the appellants' contention was not bolstered by a section of the osteopathic practice act which declares that osteopaths shall observe and be subject to state and municipal regulations relating to the control of contagious diseases, the reporting and certifying of births and deaths, and all matters relating to public health, the same as physicians of other schools (Sec. 84-1211). This language, said the court, does not broaden the definition

of an osteopath. It simply sets the requirements of others in the respects stated as a requirement for an osteopath.

The court refused to agree with the appellants' further contention that, since a license to practice osteopathy entitles the holder thereof to practice osteopathy as taught in reputable colleges of osteopathy and since the osteopathic college of which Turner was a graduate taught optometry, Turner's license authorized him to practice optometry without procuring a license under the optometry practice act. In the first place, said the court, the osteopathic practice act authorizes the practice of osteopathy, and that alone, as taught in reputable colleges of osteopathy, and optometry is not properly embraced within the meaning of osteopathy. In the second place, the osteopathic practice act was enacted in 1909 and the optometry practice act in 1916. The only persons relieved from procuring a license under the optometry act before engaging in the practice of optometry are "physicians and surgeons duly licensed to practice medicine," and osteopaths cannot be so classified. Therefore, even if originally the osteopathic practice act authorized one holding a license to practice osteopathy to practice optometry if it were taught in a reputable college of osteopathy, this rule was changed or repealed by the subsequent conflicting optometry practice act of 1916, which requires a license under that act lawfully to practice optometry. To the extent of any conflict the latter act, the optometry practice act, must govern.

Finally, said the court, a fair consideration of the various statutes of Georgia relating to the practice of medicine, the practice of optometry and the practice of osteopathy compels the conclusion that the legislature provided for the regulation and licensing of what it construed to be the practice of medicine under the medical practice act, and that although both optometry and osteopathy are arts of healing neither constitutes the practice of medicine. While the legislature has recognized osteopathy as one of the healing arts and has set up a plan for licensing osteopaths, it did not intend that osteopaths should be permitted to embrace the field of optometry and other professions by adopting the methods of healing practiced by such professions, on the theory that such methods are taught and practiced in reputable colleges of osteopathy. To construe the osteopathic practice act as urged by the appellants would mean that by merely teaching and practicing every known science of healing in osteopathic colleges an osteopath would be permitted to practice without restraint all such methods of healing. This would nullify every regulatory statute of the state having for its purpose the licensing and regulation of the practice of the various professions of healing authorized by law. Our conclusion is that Turner's license to practice osteopathy does not authorize him to practice optometry. It is conceded that if Turner's conduct is illegal, which it is, then since he is the employee and agent of Mabry this illegal practice is equally chargeable to Mabry and renders him likewise subject to an injunction.

For the reasons stated, the Supreme Court upheld the injunction of the trial court restraining Turner and Mabry from practicing optometry.—*Mabry v. State Board of Examiners in Optometry*, 10 S. E. (2d) 740 (Ga., 1940).

## Society Proceedings

### COMING MEETINGS

Annual Congress on Medical Education and Licensure, Chicago, Feb. 17-18. Dr. W. D. Cutter, 535 North Dearborn St., Chicago, Secretary.

American Orthopsychiatric Association, New York, Feb. 20-22. Dr. Norville C. La Mar, 149 East 73d Street, New York, Secretary.

Central Surgical Association, Ann Arbor, Mich., Feb. 28-March 1. Dr. George M. Curtis, Ohio State University, Columbus, Ohio, Secretary.

Middle Section, American Laryngological, Rhinological and Otolological Society, Chicago, Jan. 27. Dr. Walter H. Theobald, 307 North Michigan Blvd., Chicago, Chairman.

Mid-South Post Graduate Medical Assembly, Memphis, Tenn., Feb. 11-14. Dr. A. F. Cooper, Goodwyn Institute Bldg., Memphis, Tenn., Secretary.

Pacific Coast Surgical Association, Los Angeles, Feb. 19-22. Dr. H. Glenn Bell, University of California Hospital, San Francisco, Secretary.

Society of Surgeons of New Jersey, Newark, Jan. 29. Dr. Walter B. Mount, 21 Plymouth St., Montclair, Secretary.

Society of University Surgeons, St. Louis, Feb. 14-15. Dr. Frank Glenn, 525 East 68th St., New York, Secretary.

Western Section, American Laryngological, Rhinological and Otolological Society, San Francisco, Feb. 1-2. Dr. Robert C. Martin, 334 Post St., San Francisco, Chairman.

## Current Medical Literature

### AMERICAN

The Association library lends periodicals to members of the Association and to individual subscribers in continental United States and Canada for a period of three days. Three journals may be borrowed at a time. Periodicals are available from 1930 to date. Requests for issues of earlier date cannot be filled. Requests should be accompanied by stamps to cover postage (6 cents if one and 18 cents if three periodicals are requested). Periodicals published by the American Medical Association are not available for lending but can be supplied on purchase order. Reprints as a rule are the property of authors and can be obtained for permanent possession only from them.

Titles marked with an asterisk (\*) are abstracted below.

#### American Journal of Diseases of Children, Chicago 60:1019-1244 (Nov.) 1940

- \*Treatment of Pneumonia in Children with Single Dose of Sulfapyridine. L. Platt, New York.—p. 1019.  
Ascorbic Acid Content of Cow's Milk at Various Stages of Lactation. A. D. Holmes, F. Tripp, E. A. Woelffer, Boston, and G. H. Satterfield, Raleigh, N. C.—p. 1025.  
Neuromuscular Mechanism of the Infant: Development Reflected by Postural Adjustments to Inverted Position. Myrtle B. McGraw, New York.—p. 1031.  
Chorionic Gonadotropic Effects on Growth in Sexually Underdeveloped Older Boys. G. B. Dorff, Brooklyn.—p. 1043.  
Anthropometry in Children: Progress in Allergic Children as Shown by Increments in Height, Weight and Maturity. M. B. Cohen, R. R. Weller, Cleveland, and S. Cohen, New Orleans.—p. 1058.  
Relation of Sepsis to Infections of Upper Respiratory Tract. A. Kanof and B. Kramer, Brooklyn.—p. 1067.  
Obesity in Childhood: IV. Energy Expenditure of Obese Children. Hilde Bruch, New York.—p. 1082.  
Sexual Curiosity of Children. J. H. Conn, Baltimore.—p. 1110.  
Blood Lipid Partition in Hypothyroidism of Childhood. L. S. Radwin, J. P. Michelson, J. Melnick and S. Gottfried, Brooklyn.—p. 1120.  
\*Equine Encephalomyelitis in Infancy. R. V. Platou, Minneapolis.—p. 1155.

**Sulfapyridine in Pneumonia of Children.**—Platt states that during the winter of 1939-1940 41 ward patients admitted to the Children's Hospital with pneumonia received one large dose of sulfapyridine. Private patients continued to be treated by multiple doses. The ages of the ward patients ranged from 2 months to 12 years. A roentgen diagnosis of lobar pneumonia was made in 27 and of bronchopneumonia in 14. Pneumococci were recovered from the nasopharyngeal and gag cultures of 37 children. Thirty-four patients were treated within four days of onset. The amount of sulfapyridine given was 0.3 Gm. per kilogram of body weight (2 grains per pound), as a suspension in either milk or a formula. The maximal dose was 4 Gm. Nothing was given by mouth for four hours, after which food was given as desired and fluids were forced. The rectal temperature of 34 children dropped to 100 F., or below, within twenty-four hours after the drug was given, and in 5 the fever continued after forty hours. Two of these 5 patients died. These were the only fatalities. A mild hydrothorax, which cleared spontaneously, developed in 1 child. There were no cases of empyema. One child responded promptly to treatment, but on the fourth day the pneumonia spread to another lobe and he responded promptly to a second single dose of sulfapyridine. There was a secondary rise in temperature in 14 patients. Usually this occurred on the second or third day after chemotherapy, although in 2 it occurred on the sixth day. With this secondary elevation of temperature the children did not look particularly ill and in all but 2 the temperature was again normal within twenty-four hours. Three of these children were given additional sulfapyridine, but the defervescence seemed no more rapid than in those not treated. The cause of the secondary rise in temperature is not known but does not seem to be important clinically. The level of free sulfapyridine in the blood of 35 patients was determined and of 26 it was above 4 mg. per hundred cubic centimeters. In most instances these levels were maintained in the blood for at least eighteen hours. In some, effective levels were maintained for at least thirty hours. In the remaining 9 children the lowest level was 1.9 mg. per hundred cubic centimeters of blood. One of these children died. In the other 8 the defervescence was as prompt and the clinical course as satisfactory as in those having levels above 4 mg. No rashes, blood dyscrasias or untoward mental symptoms were observed. Transient microscopic hematuria developed in 1 child, 12 children vomited once and 8 vomited more than once. Vomiting

occurred when the children first received fluids. This vomiting did not interfere with the therapy, as by that time the sulfapyridine had passed into the intestinal tract and had been largely absorbed. Only 2 children had persistent vomiting, and 1 of these had pertussis. During the same period 24 private patients were treated by the multiple dose method. These children appeared no sicker than those in the ward. Four of 9 infants less than 1 year of age died in spite of receiving between 0.8 and 2 Gm. of sulfapyridine daily. Three children had no emesis, 3 vomited once and 18 more than once, and 4 of these vomited more than ten times. Only 1 child had a secondary rise in temperature, compared with 34 per cent in the single dose group. It appears that the single dose method simplifies the treatment and decreases toxic effects. It interferes less with the child's rest and sleep and is less demanding on the nursing staff.

**Equine Encephalomyelitis in Infancy.**—Review of literature on equine encephalomyelitis, according to Platou, suggests that the disease is a specific virus infection affecting a variety of animals, including man. Young persons are most susceptible. Its natural reservoir has not been recognized. Mosquitoes and ticks are the only proved vectors. The virus exists in the United States in at least two immunologically distinct strains. They are sharply demarcated geographically by the Appalachian Mountains. Experimentally, the course of infection with either of the strains can be divided roughly into visceral and neurotropic phases. Under natural conditions the disease in many cases may go unrecognized as abortive or poorly defined by visceral manifestations. The virus is best cultivated on the chorioallantoic membrane of the developing chick. Chick embryo vaccine treated with a solution of formaldehyde U. S. P. in wood alcohol and water seems the most practical and effective prophylactic agent for control of the disease in horses, but it has not as yet been used for the human subject. Hyperimmune serums appear to have no value in the treatment of experimental infections when given after fever has ensued. The author presents a case illustrating the postencephalitic state, probably an aftermath of infection with the virus of "equine" encephalomyelitis. The diagnosis was established by the demonstration of a high titer of antiviral antibodies for the western strain in the patient's serum six months after the initial acute infection. The mother's serum contained no protective substances against the virus. Equine encephalomyelitis should be considered in the differential diagnosis of the many obscure neurologic disorders in which mental retardation and spasticity are outstanding manifestations.

#### American Journal of Public Health, New York 30:1269-1390 (Nov.) 1940

- Public Health in National Defense. W. S. Leathers, Nashville, Tenn.—p. 1269.  
Prostitution as Source of Infection with Venereal Diseases in the Armed Forces. C. R. Reynolds, Harrisburg, Pa.—p. 1276.  
Relationship of the Health of Civilians to Efficiency of the Army. J. C. Magee, Washington, D. C.—p. 1283.  
Relationship of the Health of Civilians to Efficiency of the Navy, with Special Reference to the Venereal Disease Problem. C. S. Stephenson, Washington, D. C.—p. 1291.  
Experience of the Army and Civilian Conservation Corps in Handling Newly Mobilized Men. A. P. Hitchens, Philadelphia.—p. 1297.  
Present Status of Knowledge Concerning Influenza. F. L. Horsfall Jr., New York.—p. 1302.  
\*Typhoid Vaccine Studies: Revaccination and Duration of Immunity. D. Longfellow and G. F. Luippold, Washington, D. C.—p. 1311.  
Human Relations as a Public Health Problem. H. L. Dunn, Washington, D. C.—p. 1318.  
The Community Health Education Program: The Hartford Plan. Lucy S. Morgan and B. G. Horning, Hartford, Conn.—p. 1323.  
Population Trends and Public Health Problems. F. Osborn, New York.—p. 1331.  
Essentials of a Workable Merit System. D. C. Sowers, Boulder, Colo.—p. 1337.  
The Merit System and Public Health. H. B. Mitchell, Washington, D. C.—p. 1343.  
Health and Medical Preparedness. T. Parran, Washington, D. C.—p. 1348.  
Illness Due to Commercially Prepared Egg and Olive Sandwiches Contaminated by Probable Carrier of Hemolytic Staphylococcus Aureus. J. C. Geiger and A. B. Crowley, San Francisco.—p. 1351.

**Typhoid Vaccine Studies.**—Longfellow and Luippold report on the effectiveness of typhoid vaccination as studied at the laboratories of the Army Medical School. The study considers the duration of immunity subsequent to vaccination and that

following revaccination by the intracutaneous injection of typhoid vaccine. Revaccination is the same as initial vaccination; three subcutaneous doses, 0.5, 1 cc. and 1 cc., respectively, at approximately weekly intervals. The three doses constitute a "standard course," which is prescribed for the military service, and military personnel are required to be revaccinated at intervals of three years. Exemptions are granted after two courses and to persons more than 45 years of age. A group of 189 young adult males who had received one standard course of typhoid vaccine intracutaneously from two to three years previously were selected for study. The blood serums of all members of this group after revaccination protected mice against at least one hundred minimal lethal doses and in 95 per cent against at least one thousand minimal lethal doses of the test organisms. Another group of 51 individuals were given 0.5 cc. of vaccine subcutaneously. Members of this group had received from one to seven standard courses of vaccine, the last of which had been given from two to twenty years ago. The blood serums were titrated immediately before and two weeks subsequent to revaccination. The blood serums of all members of this group after revaccination protected mice against at least one hundred minimal lethal doses and in 92 per cent of the cases against at least one thousand minimal lethal doses of the test organism. The results obtained in these two groups were compared with the usual method of revaccination for which 50 individuals who had received from one to five standard courses of vaccine were selected. They had had the last course at least two years previously. The members of this group were given a standard course of vaccine, and their blood serums were titrated immediately before and two weeks after administration of the third dose of vaccine. After revaccination the blood serums protected mice against at least one hundred minimal lethal doses and in 96 per cent it protected mice against at least one thousand minimal lethal doses of the test organism. The authors' studies on the duration of immunity among persons vaccinated only once and two or more times indicate that in order to maintain a high degree of immunity to typhoid, as indicated by humoral antibodies, revaccination at intervals of one year appears to be an advisable procedure, and certainly that the interval should not exceed two years. Revaccinations at the intervals recommended should not be discontinued because of age or because of many previous revaccinations.

### Anesthesiology, New York

1:241-368 (Nov.) 1940

- Surgical Posture, with Symbols for Its Record on the Anesthetist's Chart. A. H. Miller, Providence, R. I.—p. 241.  
Studies of Vinethene as Anesthetic Agent. O. S. Orth, H. C. Slocum, J. W. Stutzman and W. J. Meek, Madison, Wis.—p. 246.  
Mental Disturbances Following Nitrous Oxide Anesthesia. C. T. Batten, Battle Creek, Mich., and C. B. Courville, Los Angeles.—p. 261.  
Studies with Cyclopropyl Methyl Ether (Cyprome Ether) in Man. Constance Black, G. E. Shannon and J. C. Krantz Jr., Baltimore.—p. 274.  
Total Spinal Block: Preliminary Report. CoTui, C. L. Burstein and W. F. Ruggiero, New York.—p. 280.  
Relaxation: Meditative Essay. N. A. Gillespie, Madison, Wis.—p. 292.  
Control of Gastrointestinal Tone and Motility with Novatropine. S. J. Martin and R. C. Batterman, New York.—p. 300.  
Anesthetic Potency of Some New Piperidine Derivatives. W. H. Hunt and R. J. Fosbinder, Newark, N. J.—p. 305.  
Fate of Anesthetic Drugs in the Body. J. Adriani, New York.—p. 312.  
Substances Causing Vasoconstriction. V. E. Henderson, Toronto.—p. 323.

### Archives of Pathology, Chicago

30:1159-1318 (Dec.) 1940

- Changes in Arteries in Walls of Tuberculous Pulmonary Cavities. R. Charr and J. W. Savacool, Philadelphia.—p. 1159.  
Effect of Exposure to High Oxygen Tension on Lungs and Heart of Rat. D. J. Rehbock, Mary Ruth Oldt and H. M. Dixon, Cleveland.—p. 1172.  
Effect on Prostate Gland of Occlusion of Its Ducts. C. Huggins and P. J. Clark, Chicago.—p. 1178.  
Influence of Heptaldehyde on Carcinogenic Action of Methylcholanthrene. C. Carruthers, St. Louis.—p. 1184.  
Effects of Yellow Phosphorus and Arsenic Trioxide on Growing Bones and Growing Teeth. C. O. Adams and B. G. Sarnat, Chicago.—p. 1192.  
Diplomyelia (Duplication of Spinal Cord). R. Y. Herren, Portland, Ore., and J. E. Edwards, Boston.—p. 1203.  
TriPLICATION of Large Intestine. A. W. Gray, Montreal.—p. 1215.  
Properties of Cancer Cells. E. V. Cowdry, St. Louis.—p. 1245.

### Arkansas Medical Society Journal, Fort Smith

37:135-156 (Dec.) 1940

- Premature Detachment of Normally Situated Placenta. R. M. Sloan, Jonesboro.—p. 135.  
Foreign Bodies in Food and Air Passages. P. L. Mahoney and J. S. Agar, Little Rock.—p. 140.

### Connecticut State Medical Journal, Hartford

4:707-780 (Dec.) 1940

- \*Can Diabetes Be "Cured" by Early, Vigorous Treatment? L. T. McDaniel, A. Marble and E. P. Joslin, Boston.—p. 710.  
Some Medicolegal Problems. A. F. Mignone, New Haven.—p. 719.  
Dissecting Aortic Aneurysm: Report of Two Cases. W. H. Lovell Jr., Hartford.—p. 724.  
Early Days of the Fairfield County Medical Association. W. M. Stahl, Danbury.—p. 732.  
Common Sense in Psychiatry. C. C. Burlingame, Hartford.—p. 735.  
Child Guidance. G. K. Pratt, New Haven.—p. 739.  
Diseased Cervix as Cause of Symptoms in Women. H. B. Perrins, New Haven.—p. 741.  
Pregnancy Complicated by Cancer of Cervix: Case Report. A. H. Morse, New Haven.—p. 743.

"Curability" of Diabetes.—McDaniel and his co-workers studied the records of diabetic patients in the hope of discovering any analogies between the cause of their diabetes and that produced experimentally in animals and to see if any patients could be found who seemingly were cured or had benefited by early energetic treatment. The records of those few patients were studied in whom at postmortem examination there were microscopic evidences of hydropic degeneration of the islet cells. Recent work has shown that at this stage of degeneration of islet tissue the process is reversible. The data show that, although no cures can be claimed, early, vigorous treatment in certain patients with either a restricted diet or insulin or both seems to have brought about an unexpected degree of amelioration. However, many other patients, similarly treated, responded with only the expected improvement. A review of cases in which the onset of the diabetes had been "rapid," "gradual" or even "indefinite" may show many cases in which proper treatment ameliorated the disease. Resting procedures (fasting, fat feeding and insulin) prevent the degenerative changes from occurring in cells not already affected and permit the restoration of those exhausted cells which still retain the ability to recover. This suggests a logical basis for the Naunyn dictum that a patient with severe diabetes carefully treated often does well, whereas a patient with mild diabetes, if neglected, does poorly. Degenerative factors other than infections and the diabetogenic hormone of the anterior pituitary may exist. The undiscovered factors may be more frequent in occurrence and more insidious in their action. Education of laymen, and particularly relatives of diabetic patients, is the most effective approach to shortening the interval between the onset of the disease and diagnosis. Yearly physical and urinary examinations should be done, and companies insisting on regular, routine examination of their employees are doing them a kindness. All school children should have yearly examinations. Relatives of diabetic persons should be examined even more frequently and should have periodic blood sugar tests. The importance of obesity and heredity should never be slighted or neglected. Haist, Campbell and Best suggest the prophylactic administration of insulin and a low carbohydrate, high fat diet for large groups of persons with potential diabetes (children of diabetic families). The authors suggest that a feasible way to test the validity of experimental observations is to start the nondiabetic twin of similar twins on insulin as soon as the diagnosis is made in one of them, since the disease will eventually develop in the other one. Prophylactic treatment would also be of equal value in children of conjugal diabetic persons. Protamine zinc insulin by its continuous release of active insulin affords the constant effect of a protective mechanism. All diabetic children should take at least a small daily dose of protamine zinc insulin. A good response to initial treatment is never an indication for a rapid reduction of insulin or its omission, for the neglect of diet or for the toleration of obesity. The authors state that diabetes is never "complete" until death occurs—there are always some functioning islet cells and to keep them in a functioning state is the main goal of treatment. If a patient with diabetes of recent and rapid onset presented himself, the authors would immediately begin vigorous treatment with insulin and a low



carbohydrate diet with the required calories made up in fat. If after a few weeks there was no significant amelioration they would increase the diet to one of moderate carbohydrate restriction, assuming that by this time all the beta cells which could recover had done so. They would be extremely slow in reducing the insulin dosage and diligent in its use with intermittent infections. They believe that a diabetic patient should be taught to guard his islet tissue as he does his toes and limbs.

### Delaware State Medical Journal, Wilmington

12:231-244 (Nov.) 1940

Right Paraduodenal Hernia. W. E. Bird, Wilmington.—p. 231.

### Georgia Medical Association Journal, Atlanta

29:475-518 (Oct.) 1940

Use of Pentothal Sodium-Oxygen Anesthesia as a Total Anesthetic Agent in Major Surgical Procedures. T. C. Davison and F. F. Rudder, Atlanta.—p. 475.

Therapy of Menometrorrhagia: I. Study of Mechanism of Uterine Bleeding; II. Study of Postpartum Period. R. B. Greenblatt, Augusta.—p. 481.

Functional Heart Disease. J. A. Redfearn, Albany.—p. 486.

Therapy of Third, Fourth and Fifth Venereal Diseases. M. T. Benson Jr. and J. A. Henry, Atlanta.—p. 489.

Carcinoma of the Prostate. M. L. Boyd and J. B. Nuckolls, Atlanta.—p. 493.

Pancreatitis: Report of Cases. G. J. Dillard, Columbus.—p. 499.

Further Observation on Antenatal Use of Quinine. L. Smith, Atlanta.—p. 502.

Rocky Mountain Spotted Fever: Case Report. A. Chappell, Atlanta.—p. 504.

Treatment of Body Fluid Loss. F. K. Boland, Atlanta.—p. 505.

### Iowa State Medical Society Journal, Des Moines

30:565-626 (Dec.) 1940

State and City Wide Plans for Care of Premature Infant. J. H. Hess, Chicago.—p. 565.

Use of Burbot Liver Oil Intramuscularly for Ocular Avitaminosis A. H. C. Kluever, C. H. Coughlan and L. M. Martin, Fort Dodge.—p. 575.

Obstacles to Effective Control and Prevention of Scarlet Fever. G. W. Anderson, Minneapolis.—p. 580.

The 1939 Poliomyelitis Epidemic in the City of Des Moines. E. M. George and H. E. Ransom, Des Moines.—p. 584.

Observed Relationship of Poliomyelitis Incidence and Environmental Sanitation in Des Moines, Iowa. R. C. Hanlon, Des Moines.—p. 587.

Ophthalmologists and Elementary Education. G. C. Albright, Iowa City.—p. 590.

Diagnosis and Treatment of Paroxysmal Tachycardia in General Practice. O. Neurath, Sigourney.—p. 596.

### Journal of Allergy, St. Louis

12:1-116 (Nov.) 1940

Cholinesterase in Blood of Allergic Patients. R. C. Hawes and G. A. Alles, Los Angeles.—p. 1.

Quantitative Measurement of Whealing in Hypersensitivity to Cold Treated with Histamine and Histaminase. F. E. Maisel and H. A. Abramson, New York.—p. 6.

Snake Venom and Allergy. H. G. Golan, Richmond Hill, N. Y.—p. 11.

Time Required for Production of Hay Fever by Spores of Newly Encountered Fungus, Johnson Grass Smut. E. W. Phillips, Phoenix, Ariz.—p. 24.

Erythema Nodosum from Sulfanilamide: Some Experimental Aspects. A. B. Loveman and F. Simon, Louisville, Ky.—p. 28.

\*Food Sensitivity as Factor in Etiology of Acne Vulgaris. F. E. Cormia, Montreal.—p. 34.

Allergic Rhinitis and Asthma Due to Sensitization to the Mexican Bean Weevil (Zabrotes Subfasciatus Boh.). F. W. Wittich, Minneapolis.—p. 42.

Relationship of Mold Reactions to Clinical Symptoms. R. Chobot, H. Dundy and N. Schaffer, New York.—p. 46.

Clinical Comparison of Epinephrine in Oil and Epinephrine in Gelatin. M. Kalmon, Akron, Ohio.—p. 55.

**Food Sensitivity and Acne Vulgaris.**—Cormia suspected food sensitivity in 25 of 80 private patients with acne vulgaris. Twenty of them were given elimination diets. Twelve additional patients, all with severe acne of two or more years but lacking a history of food sensitivity were included as a basis for comparison. Skin testing with the common food allergens was done in 13 of the 32 from 15 to 34 years of age who had had acne from two to seventeen years. The results were checked against those obtained with the elimination diets. There was a family history of acne and seborrhea in 22, of infection in 17 and a definite history of atopy in only 10 families. The chief aggravating factors were inadequate rest, menstrual periods and alcohol. Sixteen patients believed that one or more foods caused flare-ups.

All patients were placed on elimination diets; roentgen therapy was used but was delayed until food testing was nearly complete, and endocrine therapy was given when indicated. The foods most frequently mentioned were chocolate and tomatoes. Other foods incriminated were pork, potatoes, cheese, bread, eggs, apples, tea, coffee and oranges. Of the twenty-four foods listed by 16 patients, thirteen caused a flare-up of the eruption on ingestion. Four patients would not be tested by ingesting the specific food because of previous severe reactions. Generally the patients who reacted most vigorously to the ingestion tests gave positive intradermal reactions to the food in question. After the eruption improved, the foods were gradually reintroduced into the diet, and only rarely did they cause subsequent reactions. The foods, in order of frequency, causing demonstrable flare-ups were chocolate, tomatoes, nuts, spinach, wheat, white bread, coffee, potato, eggs, peas, grapefruit, milk, string beans, tea, beef, oatmeal, fish, corn, carrot, lettuce, beet, cheese and cabbage. Four patients reacted positively to white bread but gave negative reactions to wheat. This is confirmatory evidence that bread improvers containing bromates could be responsible for flare-ups (Wise and Sulzberger). Food elimination diets were curative in 2 patients, showed from 75 to 90 per cent improvement in 5 and from 50 to 75 per cent improvement in 8. The observation period was from one to three years.

### Journal of Nutrition, Philadelphia

20:519-646 (Dec.) 1940. Partial Index

Multiple Deficiencies in Modified Goldberger Diet as Demonstrated with Chicks. H. A. Waisman and C. A. Elvehjem, Madison, Wis.—p. 519.

Pantothenic Acid Requirement of Rat. K. Unna, Rahway, N. J.—p. 565.

Effect of Vitamins A and C on Experimental Hyperthyroidism. I. J. Belasco and J. R. Murlin, Rochester, N. Y.—p. 577.

Influence of Exercise on Growing Rat in Presence and Absence of Vitamin B<sub>1</sub>. N. B. Guerrant and R. A. Dutcher, State College, Pa.—p. 589.

Studies on Dermatitis in Chicks Distinct from Pantothenic Acid Deficiency. D. M. Hegsted, J. J. Oleson, R. C. Mills, C. A. Elvehjem and E. B. Hart, Madison, Wis.—p. 599.

### Journal of Pharmacology & Exper. Therap., Baltimore

70:245-322 (Nov.) 1940. Partial Index

Histologic Effects of Intraneural Injections of Quinine Compounds. R. Salm, Edinburgh, Scotland.—p. 245.

Studies on Purified Digitalis Glucosides: II. Potency and Dosage of Lanatoside C in Man. N. T. Kwit, H. Gold and M. Cattell, New York.—p. 254.

Further Observations on Influence of Dietary Protein on Toxicity of Selenium. M. I. Smith and E. F. Stohlgman, Washington, D. C.—p. 270.

Thiamine in Treatment of Morphine Abstinence Syndrome in Man. C. K. Himmelsbach, Lexington, Ky.—p. 293.

Emptying Time of Normal Human Stomach as Influenced by Sulfapyridine. D. W. Northup and E. J. Van Liere, Morgantown, W. Va.—p. 297.

### New England Journal of Medicine, Boston

223:835-876 (Nov. 21) 1940

Organization of Psychiatric Clinic in Outpatient Department of a General Hospital. R. Fleming, G. P. Coon, A. W. Contratto, J. M. Flynn, C. R. Atwell and Gerna S. Walker, Boston.—p. 835.

\*Cancer of Stomach. H. M. Clute and T. J. Anglem, Boston.—p. 839.

\*New Type of Medication to Be Used in Bronchial Asthma and Other Allergic Conditions: Preliminary Note. E. A. Brown, Boston.—p. 843.

Diverticulitis. J. F. Erdmann, New York.—p. 846.

\*Radiation Treatment of Plantar Warts. J. H. Marks and C. C. Franzen, Boston.—p. 851.

War-time Preventive Medicine. C. A. Janeway, Boston.—p. 854.

**Cancer of Stomach.**—During the five years ended January 1940 Clute and Anglem treated 68 patients diagnosed preoperatively as having gastric cancer. On exploration 5 presented benign or no lesion. Of the remaining 63, 11 were not suitable for exploration, 19 on exploration were found inoperable, 8 were suitable for only palliative operations and 25 had resection. Of the 27 resectable lesions, including 2 that were benign or borderline, 2 were so extensive as to require total gastrectomy. The postoperative mortality was 15 per cent. Three of the deaths were from peritonitis and 1 from bronchopneumonia. The 2 patients on whom total gastrectomies were performed were alive twenty months after operation. One of them has not been observed, but he reports that he feels well and works every

day. The other patient was recently reoperated on for bilateral Krukenberg ovarian tumors, and several small metastatic peritoneal implants were observed. In 1935, 1936 and 1937, 12 patients survived resection. Although 7 of these lived for two years or more, all but 1 is now either dead or has a definite recurrence. In 1938 and 1939, 11 successful resections were done. All the patients are still alive, although 2, who have lived twenty months following operation, have a recurrence. The results show that preoperative diagnosis cannot be over-emphasized. The inability of the roentgen diagnostician to differentiate definitely between ulcer and cancer may easily lead to undesirable delay in instituting proper therapeutic measures. When the roentgenogram suggests cancer, immediate surgery is preferable to delay and repeated roentgen examination. Long delays must be avoided. Accuracy of diagnosis should embrace the separation not only of malignant from nonmalignant lesions but also operable from inoperable cases. The criteria that indicate inoperability are the presence of a large fixed mass, ascites, involvement of the cardiac opening of the stomach, a roentgenogram showing the stomach drawn close to the spine or to the right of it, a large nodular liver and distant metastases. When any doubt as to operability exists exploration should be done, for often cases that preoperatively appear to be doubtful are on exposure readily operable. The development of peritoneoscopy may aid in the recognition of inoperable cases that in the past have come to exploration.

**New Medication for Asthma and Other Allergies.**—Brown suggests the use of capsules containing  $\frac{1}{2}$  grain (0.032 Gm.) of ephedrine sulfate,  $\frac{1}{2}$  grain of sodium phenobarbital and 3 grains (0.2 Gm.) of theophylline sodium acetate for symptomatic or prophylactic treatment of nocturnal bronchial asthma. He has used this medication in 189 cases of bronchial asthma and also for other allergic complaints. The asthma in the cases reported was extrinsic in 80, intrinsic in 50 and mixed in 10 cases. In every case in which the usual doses of ephedrine and phenobarbital were adequate the capsule described was equally or more effective. Thirteen patients complained of side reactions to the ephedrine. Six patients complained of nausea and indigestion. This was found to be due to the theophylline sodium acetate, and they were given capsules without this component. Sensitivity to phenobarbital was not encountered, and there was no case of a sedative "hangover" due to the phenobarbital. Two patients complained that all gelatin capsules caused pyrosis. The dosage having been stabilized, an enteric coating planned to dissolve in from four to five hours was manufactured. It contained cetyl alcohol, gum mastic, tolu balsam, gelatin, acacia and sugar. Acetone, alcohol and water were used as solvents. The enteric coated tablets were given to 117 patients, 61 of whom also received the plain capsule as their asthma occurred during the day, during the first four hours after retiring or during both periods. The remaining 56 patients had asthma only four or more hours after retiring and were given only the enteric coated capsules. Of the 117 patients, 8 complained of waking six hours after medication. They were free of asthma but unable to fall asleep again. This was attributed to the theophylline, and either it was omitted or additional phenobarbital was given. The patients with asthma during both day and night showed the best improvement. The ability to sleep during the night lessened the number or intensity of their daily attacks. This was especially true of the intrinsically asthmatic patients. Not all patients got relief at all times. Those with severe attacks who were not helped formerly by ephedrine and phenobarbital alone were only occasionally benefited by the capsules and tablets. The new medication was definitely more effective in patients with moderate and mild symptoms.

**Radiation Treatment of Plantar Warts.**—Marks and Franseen stress the need of careful search for a wart in any painful callus. Such warts do not project above the surrounding skin on weight-bearing surfaces but are flat and usually surrounded by callus formation. Small, reddish or brownish black dots may be seen through the callus or will become evident by moistening the callus or paring away the less translucent superficial layers. These dots represent the capillary loops of the wart. At the Palmer Memorial Hospital irradiation has given a high percentage of satisfactory results. However, dur-

ing the last two years a number of unfortunate results from roentgen and radium treatment have come to the authors' attention and suggested an analysis of the 175 cases treated between January 1930 and May 1939. The primary treatment of 138 cases was by radium: once in 115 cases, twice in 26 and three or more times in 8. The primary radium treatment failed in 9 and was followed by some other method. Twenty-nine of the radium-treated patients returned for examination, and 22 were cured: 16 after one treatment and 6 after two or more treatments. Of the 6 patients treated two or more times, 2 had minor atrophic changes in the skin and 1 had marked atrophy at the site of treatment and likely to lead to a radiation ulcer at a later date. Radium treatment did not result in cure in 7; 1 was cured by electrodesiccation and 1 by excision, 1 had a persistently painful wart within an area of atrophy and 4 later received roentgen therapy. Since 1937, 15 patients have been treated primarily by roentgen rays. All these patients were reexamined one year or more after treatment; 10 showed complete cure (with only 1 showing slight cutaneous atrophy at the treatment site), 1 with a wart on the great toe had such marked atrophy that amputation of the toe became necessary when ulceration occurred after trauma, 1 showed a small remnant of the original wart but was symptom free and 3 failed to obtain cure but were later treated successfully by electrodesiccation. Of 6 patients who had roentgen treatment following failure of radium, only 2 had satisfactory end results. The remaining 4 had radiation ulcers necessitating surgical procedures to replace the damaged tissues. Excision of the area of ulceration followed by plastic repair was required by 3 and the toe of 1 was amputated. All had received two or more radium treatments followed by roentgen treatment and had been treated over periods of five, five, nine and eleven years, respectively. The experiences of these patients indicate that repeated heavy doses of roentgen rays or radium should not be employed in treating plantar warts. A long interval between treatments increases rather than decreases the danger. The authors believe that many enthusiastic recommendations of radiation treatment are based on follow-ups made too soon after treatment and before the late end results are known. Although symptoms may be relieved, the condition may recur later and with large doses or repeated treatments there is always danger of late adverse radiation effects. The area so treated by large single doses should not exceed 1 cm. in diameter: 16 millicurie hours of radon filtered through 0.3 mm. of steel and from 1,200 to 1,800 roentgens, depending on the site and size of the lesion. Larger doses are required when the wart is in the tougher tissues of the ball of the foot. If a single radiation treatment fails to cure, the method should be discontinued. Electrodesiccation, when properly carried out, gives excellent results. The absence of late after-effects and the certainty of complete eradication if done thoroughly under adequate local anesthesia compensate for the slight immediate discomfort. It is essential to desiccate thoroughly the soft, active base of the wart that lies deep beneath the callus. In all cases in which radiation has failed, electrodesiccation has succeeded in eradicating the wart.

#### North Carolina Medical Journal, Winston-Salem

1:579-630 (Nov.) 1940

- \*Clinical Observations on Local Use of Sulfanilamide in Dentistry. J. A. Sinclair, Asheville.—p. 579.
- Orbital Tumors and Their Surgical Treatment. A. B. Reese, New York.—p. 583.
- Clinical Interpretations and Applications of Electrocardiograms. V. S. Caviness, Raleigh.—p. 592.
- Joint Responsibility for Maternal Welfare in the Light of Current Social Trends. W. Z. Bradford, Charlotte.—p. 597.
- Endometriosis. W. B. Bradford, Charlotte.—p. 600.
- The Blood Bank. R. B. Davis, Greensboro.—p. 606.
- New Conception of Essential Hypertension. F. B. Marsh, Salisbury.—p. 608.
- It May Be Helminths. C. A. Willis, Candler.—p. 613.
- Dry Ice Treatment for Hiccup. M. A. Pittman, Wilson.—p. 615.

**Local Use of Sulfanilamide in Dentistry.**—According to Sinclair, sulfanilamides have been employed in cellulitis, acute osteomyelitis and infected compound fractures. Acute necrotic gingivitis (Vincent's infection) does not respond well to sulfanilamide, and its use in chronic osteomyelitis is questionable. His clinical observations on the local use of sulfanilamide dur-

ing the last three years following all extractions and operations justify their continued use. No local toxic effect has been encountered. Roentgenograms of sockets thus treated show a normal filling in of bone substance. Swelling or fever has not been observed following extraction of teeth. Healing during this therapy has been normal. Sulfanilamide will not prevent autolysis of the blood clot (dry socket) when excessive trauma has been produced during extraction of teeth with roots embedded in a sclerosed area of bone. Interosseous circulation is scanty in this area, if present at all. Sulfanilamide is unable to prevent the "dry socket" under this condition, but it does prevent pain and hastens healing by controlling infection. Such lesions are similar to compound fractures after they have been reduced. So far the author has not observed any drug incompatible with sulfanilamide when both are used locally. Sulfanilamide placed in the socket of a recently extracted tooth does not cause a true *in vivo* or *in vitro* state, but it is nearer the *in vitro* condition. There is no circulation within the area until granulation begins, although there is a migration of leukocytes and serum seepage into the area. Because of the noncirculatory status of the area, the value of systemic administration is questionable. The placing of a part of a tablet into the socket enables it to take up its maximal concentration of sulfanilamide. This maximal saturation is maintained by the excess chemical. This is also true of a compound fracture or of osteomyelitis. Sulfapyridine has not been found superior to sulfanilamide, and the author has discontinued its use.

### Ohio State Medical Journal, Columbus

36:1249-1368 (Dec.) 1940

- Clinical and Experimental Aspects of Mode of Action of Sulfanilamide-Sulfapyridine Compounds. R. R. Mellon, Pittsburgh.—p. 1265.  
Influence of Overcrowding on Incidence of Pneumonia. J. E. Benjamin, J. W. Ruegger and Fanny A. Senior, Cincinnati.—p. 1275.  
Treatment of Disorders of Thyroid. R. A. Ramsey, Columbus.—p. 1282.  
Complications About Eye in Acute Infectious and Contagious Diseases. J. A. Toomey, Cleveland.—p. 1287.  
Empyema Thoracis: Method of Treatment by Continuous Tidal Irrigation and Drainage. J. Greenfield, Cleveland, and G. M. Curtis, Columbus.—p. 1291.  
Special Education for the Physically Handicapped. Hazel C. McIntire, Columbus.—p. 1297.  
Sterility. C. W. Pavey, Columbus.—p. 1299.  
Use and Abuse of Cesarean Section. D. D. Forward, Ashtabula.—p. 1305.  
Congenital Deformity of Trachea. J. J. Marek, Cleveland.—p. 1308.  
Anemias of Infancy and Childhood. C. R. Rittershofer, Cincinnati.—p. 1309.

### Oklahoma State Medical Assn. Jour., Oklahoma City

33:1-58 (Oct.) 1940

- Multiple Polyposis of Gastrointestinal Tract: Case Report. F. A. Glass, Tulsa.—p. 1.  
Diverticulotomy. A. L. Clark, Oklahoma City.—p. 3.  
Brain Tumors I've Met. E. H. Coachman, Muskogee.—p. 7.  
Liver Damage. T. H. McCarley, McAlester.—p. 10.  
Osteomyelitis as Cause of Crippling in Children. W. K. West, Oklahoma City.—p. 13.  
The Freedom of Science. L. J. Moorman, Oklahoma City.—p. 15.

### Philippine Medical Association Journal, Manila

20:567-636 (Oct.) 1940

- Hematologic Findings in Chronic Hemolytic Anemia (Familial Jaundice). R. J. Navarro and J. R. Cruz, Manila.—p. 567.  
First Three Years of Weekly Staff Clinical Conferences. J. Albert and P. Ignacio, Manila.—p. 573.  
Time Element in Conduct of Child Health Clinics. T. M. Gan and A. Cruz, Manila.—p. 605.

### Psychoanalytic Quarterly, Albany, N. Y.

9:453-602 (Oct.) 1940

- Utilization of Early Current Dreams in Formulating Psychoanalytic Cases. L. J. Saul, Chicago.—p. 453.  
Contribution to the Psychoanalysis of Extreme Submissiveness in Women. Annie Reich, New York.—p. 470.  
Four Types of Neurotic Indecisiveness. E. Bergler, New York.—p. 481.  
Experiences in Psychoanalytic Treatment of Psychotics. D. M. Bullard, Rockville, Md.—p. 493.  
Aggression in Rescue Fantasy. R. Sterba, Detroit.—p. 505.  
Psychologic Significance of Du and Sie. W. V. Silverberg, New York.—p. 509.  
Society and the Individual. G. Röheim, Worcester, Mass.—p. 526.

### Public Health Reports, Washington, D. C.

55:1977-2040 (Nov. 1) 1940

- Frequency and Volume of Doctors' Calls Among Males and Females in 9,000 Families, Based on Nationwide Periodic Canvasses, 1928-1931. S. D. Collins.—p. 1977.

55:2041-2098 (Nov. 8) 1940

- Teaching of Social Medicine in Liberal Arts Colleges and Universities. J. Hirsh and Elizabeth G. Pritchard.—p. 2041.  
Accidents in the Urban Home as Recorded in the National Health Survey. R. H. Britten, Joan Klebba and D. E. Hailman.—p. 2061.

55:2099-2142 (Nov. 15) 1940

- Studies of Acute Diarrheal Diseases: IV. Outbreak of Bacillary Dysentery Due to "Newcastle Dysentery Bacillus." A. V. Hardy, S. Frant, S. W. Jarcho and E. G. Schlosser.—p. 2101.  
Experimental Production of Agglutinins for *Trypanosoma Cruzi*. A. Packchianian.—p. 2116.  
Highly Virulent Strains of Rocky Mountain Spotted Fever Virus Isolated from Ticks (*Dermacentor Variabilis*) in Georgia. G. D. Brigham and J. Watt.—p. 2125.  
Disabling Morbidity Among Industrial Workers, Second Quarter and First Half of 1940, with Note on Occurrence of Bronchitis, Pneumonia and Appendicitis, 1931-1940. W. M. Gafafer.—p. 2127.

55:2143-2194 (Nov. 22) 1940

- Comprehensive Study of Influenza in a Rural Community. E. R. Rickard, E. H. Lennette and F. L. Horsfall Jr.—p. 2146.  
Sanitary Log for American Ships: Description and Plan of Operation. G. C. Sherrard.—p. 2167.  
\*Pneumonic Plague in Ecuador During 1939. J. R. Murdock.—p. 2172.  
Period of Antibody Development to Lymphocytic Choriomeningitis in Mice. R. A. Lyon.—p. 2178.

**Pneumonic Plague in Ecuador During 1939.**—Murdock states that during 1939 three outbreaks of pneumonic plague occurred in Ecuador. The first occurred during January and February in Riobamba and caused 17 deaths, the second during April in Cumbura caused 14 deaths; both of these were in the province of Chimborazo. The third outbreak, which occurred during September, started in Cofradia near Catacocha and extended to the city of Loja in the province of Loja. It caused at least 7 deaths. From the first two outbreaks there was no definite proof that secondary pneumonia developed in the patients with bubonic plague, but in Loja the history was definite; there the first primary case of plague pneumonia was diagnosed and followed through. Bubonic plague has been present in Ecuador since 1908. It has spread from the ports to the mountain districts along the rivers, railroads, highways and mule trails. The Norway rat (*Rattus norvegicus*), the Alexandrinus (*Rattus alexandrinus*) and *Rattus rattus* have been the responsible hosts. From them the disease has spread to domestic guinea pigs, wild rats (*Ratus de campo*), rabbits (*conejos*), squirrels (*ardillas*) and probably other rodents. The best methods to control and break the chain of an outbreak are rigid isolation of the infected patients with the recognition of the first suggestive symptom, strict quarantine of all persons who have been in direct contact with an infected person or persons, protection of nurses and doctors in attendance by suitable head masks, gowns and rubber gloves, thorough disinfection and fumigation of quarters occupied by the patients and a house to house inspection of infected sectors, with temperature taken twice daily and isolation of all who have a fever regardless of cause. It is the author's opinion that outbreaks of pneumonic plague result from cases of bubonic plague in which secondary pneumonia develops. This was the case in the Loja outbreak. Physicians and health officers in any endemic plague region should suspect all patients with pneumonic symptoms and especially those who die in less than four days. Patients with pneumonic plague may cough but little, the cough is soft and easy, and the sputum in the early stages may contain small flecks of pus and become blood stained only in the last stages of disease, but it is extremely cohesive and forms long, fine filaments when a portion of it is separated from the mass specimen.

### Rhode Island Medical Journal, Providence

23:163-180 (Oct.) 1940

- The Care of the Patient with Peptic Ulcer. E. S. Emery Jr., Boston.—p. 163.  
Usher Parsons, a Founder of the Rhode Island Hospital. A. H. Miller, Providence.—p. 168.

## Rocky Mountain Medical Journal, Denver

37:797-924 (Nov.) 1940

- Principles of Management of Infections of Hand. M. L. Mason, Chicago.—p. 814.  
 New Deal Medicine Man. L. E. Likes, Lamar, Colo.—p. 824.  
 Public Relations and the Medical Profession. J. B. Farley, Pueblo, Colo.—p. 830.  
 Obesity: Its Significance and Treatment. C. F. Kemper, Denver.—p. 835.

37:925-1028 (Dec.) 1940

- Objectives of American Medicine. N. B. Van Etten, New York.—p. 942.  
 Role of Voluntary Hospitals in a National Emergency. A. F. Emch, Chicago.—p. 948.  
 Lesions of Hip in Childhood and Adolescence and Their Relation to Lesions of Hip in the Adult. R. K. Ghormley, Rochester, Minn.—p. 956.  
 Subdiaphragmatic Abscess of Amebic Origin: Brief Review of Literature. O. J. La Barge, New Orleans.—p. 961.  
 Obstetric Hemorrhages. E. L. King, New Orleans.—p. 970.  
 Screen Test Developed in Laboratory of the Colorado State Board of Health in the Serology of Syphilis. W. C. Mitchell, Denver.—p. 977.

## Southern Medical Journal, Birmingham, Ala.

33:1241-1376 (Dec.) 1940. Partial Index

- Collapse Therapy in a State Tuberculosis Program. E. C. Harper, Richmond, Va.—p. 1241.  
 Nonsurgical Management of Lung Abscess. H. E. Johnson, Nashville, Tenn.; W. Pyle, Franklin, Tenn., and H. J. Shull, Shelbyville, Tenn.—p. 1245.  
 New Industrial Chemical Dermatitis. K. O. Stingily, Meridian, Miss.—p. 1268.  
 \*Diethylstilbestrol: Clinical Evaluation of Various Modes of Administration. R. B. Greenblatt, R. Torpin and W. R. Brown, Augusta, Ga.—p. 1276.  
 Cause of Menstruation and Uterine Bleeding: New Theory. K. J. Karnaky, Houston, Texas.—p. 1285.  
 Use of Diethylstilbestrol in Treatment of Menopausal Syndrome. H. S. Everett and H. G. Bennett Jr., Baltimore.—p. 1290.  
 Effect of Diet on Red Cell and Hemoglobin Formation, Blood Nitrogen and Albuminuria. H. M. Doles, Norfolk, Va.—p. 1298.  
 \*Blood Potassium Studies in Allergic States: Relation to Potassium Therapy. F. P. Parker, Emory University, Ga.—p. 1301.  
 Thyroid in Allergy: Preliminary Report Based on Study of Basal Metabolic Rates and Cholesterol Determinations in Group of Allergic and Nonallergic Patients. M. C. Barnes, Waco, Texas.—p. 1310.  
 Hypothyroidism as Etiologic Factor in Seasonal Dermatitis. J. E. Hubbard and W. B. Martin, Huntington, W. Va.—p. 1312.  
 Importance of Psychogenic Factors in Treatment of Allergic Disturbances. O. C. Hansen-Pruss, Durham, N. C.—p. 1317.  
 Chorea of Infectious Origin. E. F. Reaser, Huntington, W. Va.—p. 1324.  
 Carbohydrate Metabolism in Presence of Infection. J. O. Lisenby, Atmore, Ala.—p. 1328.  
 Focal Infection in Relation to Cardiovascular Disease and Disorder Among Railroad Employees. G. I. Jones, Washington, D. C.—p. 1330.  
 External Ear Disease, with Special Reference to Fungous Type. B. H. Minchew, B. E. Collins and M. M. Harris, Waycross, Ga.—p. 1345.

**Diethylstilbestrol.**—Between March 1939 and February 1940 Greenblatt and his associates used diethylstilbestrol for 79 patients requiring estrogen therapy. The routes of administration were parenteral, oral, vaginal and percutaneous. The dosages employed were as a rule aimed at symptomatic relief and not to test tolerance. Each of the various routes of administration has shown itself practical in maintaining a high estrogenic level. When administered parenterally its effect was not so sustained as that of estradiol benzoate. Eleven per cent of the patients receiving diethylstilbestrol parenterally experienced some nausea. The oral route, with either plain or enteric coated tablets, proved unsatisfactory as more than 50 per cent experienced undesirable side effects. Diethylstilbestrol dissolved in alcohol and used as a percutaneous rub, though not so effective, proved a convenient mode of administration. Undesired side reactions were reduced to a minimum. The most effective method of administration was vaginal suppositories. As little as 0.1 mg. in suppository form administered nightly to patients with menopausal syndrome frequently transformed the vaginal smear from castrate to a positive estrus in seven days with alleviation of menopausal symptoms. Although 26 per cent of this group experienced side effects, they were never severe, amounting only to slight vaginal soreness or mild nausea. Side effects are probably central in origin. Local irritation of gastric and intestinal mucosa evidently plays a contributory role in gastrointestinal disturbances. In most patients who exhibited side effects a tolerance developed when the dosage was reduced

or its mode of administration changed. Stilbestrol was well tolerated and proved particularly efficient in the suppression of lactation. The drug is quickly absorbed and eliminated, and therefore medication should be tapered off slowly in the treatment of this condition.

**Blood Potassium in Allergy.**—Parker determined blood serum potassium levels of 28 normal and 35 allergic patients suffering from vasomotor rhinitis, eczema, hay fever, urticaria and asthma. The values of the forty-seven determinations performed on the 28 normal individuals ranged from a low of 16.5 to a high of 21 mg. per hundred cubic centimeters; the average value was 18.47 mg. This average falls slightly below the range of from 19 to 21.2 mg. as given by MacCallum but agrees in general with a majority of normal values reported. Only 4 per cent of the determinations fell outside the range of from 16 to 20 mg. Repeated basal determinations of four normal persons were made at weekly intervals and they suggest that there exists, in each normal person, a basal potassium level from which little deviation occurs and that normal levels in different individuals generally fall within a somewhat wider range. The basal determinations among the 35 allergic persons, all of whom were showing some active manifestation of their allergic state at the time of the test, ranged from a low of 13.9 to a high of 22.8 mg. per hundred cubic centimeters. The average of the group was 18.25 mg. The potassium levels of those persons having asthma and hay fever were usually above the average, while those with eczema and vasomotor rhinitis were below. The 35 patients (with one exception) were then given either potassium chloride or potassium gluconate daily by mouth, serum potassium determinations were made at intervals of from seven to fourteen days and the daily dose of potassium was increased in accordance with the degree of relief experienced. The effective daily dose of potassium was from 15 grains (1 Gm.) to 60 grains (4 Gm.) of the chloride and from 45 grains (3 Gm.) to 125 grains (8.3 Gm.) of the gluconate. Of the 34 persons receiving treatment, 22 showed marked or complete relief of symptoms, 4 moderate relief, 4 slight improvement and 4 experienced no beneficial effect. The degree of relief appeared to be in proportion to the daily potassium intake in any single patient, since decrease of the size of the daily dose or its omission for only two days resulted in recurrence of symptoms, which again disappeared when the effective dose was resumed. The degree of relief has been sustained by all patients, in the majority of whom the observation period was from six to eleven months. There were no cumulative effects. Patients with asthma, hay fever and vasomotor rhinitis derived about equal benefit from potassium therapy while those with eczema showed little improvement. This suggests a different mechanism in the atopic and nonatopic allergic conditions. The two potassium preparations were equally effective. The effective agent appears to be the potassium ion irrespective of the radical to which it is attached. Failure with potassium iodide is readily apparent, since the maximal daily dose of potassium iodide which may be tolerated by the average person contains only half the amount of potassium present in the minimal daily dose of potassium chloride or gluconate. Repeated serum potassium determinations of 27 of the 35 allergic patients during the course of therapy showed a relationship to exist between the average serum potassium variation after potassium therapy and the degree of relief obtained. Those persons experiencing the greatest relief showed the least rise. Failure of the serum potassium to rise after therapy suggests an effective increase in the concentration of tissue potassium.

## Southern Surgeon, Atlanta, Ga.

9:775-852 (Nov.) 1940

- Treatment of Malignant Tumors of Skin. G. T. Pack and W. O. Wuester, New York.—p. 775.  
 Miller-Abbott Tube for Intestinal Feeding. L. J. Hahn and A. H. Glick, New York.—p. 797.  
 Primary Pneumococcal Peritonitis in an Adult: Recovery Following Specific Serum Treatment. W. D. Owens, Miami Beach, Fla.—p. 804.  
 Pathology Causing Sciatic Syndrome. E. Walker, Atlanta, Ga.—p. 823.  
 Spinal Anesthesia: Observations After Ten Years' Experience; Report of More Than 7,000 Cases. M. J. Tendler, Memphis, Tenn.—p. 827.  
 Carcinoma of Descending Colon. T. A. Pressly, San Antonio, Texas.—p. 836.  
 Wound Healing. W. C. Tenery, Waxahachie, Texas.—p. 843.

**Southwestern Medicine, El Paso, Texas****24:357-392 (Nov.) 1940**

- Carcinoma of Breast: Surgeon's Point of View. E. P. Palmer, Phoenix, Ariz.—p. 357.  
Central Fractures of Neck of Femur: Treatment by Internal Fixation. W. C. Campbell and H. Smith, Memphis, Tenn.—p. 361.  
Treatment of Perforated Gangrenous Appendix with Spreading Peritonitis. B. F. Stevens, El Paso, Texas.—p. 363.  
Diagnosis and Treatment of Peptic Ulcer with Special Note on Gastroscopy. A. L. Levin, New Orleans.—p. 365.  
Food Poisoning Due to Aerobacter Cloacae. R. A. Greene, Tucson, Ariz.; Z. B. Neon, Nogales, Ariz., and H. B. Harding, Tucson, Ariz.—p. 370.  
Narcolepsy: Case Report. J. W. Myers, Albuquerque, N. M.—p. 372.

**Virginia Medical Monthly, Richmond****67:717-776 (Dec.) 1940**

- Treatment of Pernicious Vomiting of Pregnancy. F. C. Irving, Boston.—p. 717.  
Treatment of Acute Deliriums. K. M. Bowman, New York.—p. 724.  
Classification of Commercial Preparations of Sex Hormones: II. W. G. Crockett, Richmond.—p. 732.  
Hepatic Physiology. R. J. Main, Richmond.—p. 739.  
Clinical Aspects of Jaundice. W. B. Martin, Norfolk.—p. 742.  
Use of Sulfanilamide Powder in Open Wounds. M. Johnson Jr. and F. F. Davis, Roanoke.—p. 748.  
Results of Treatment of Malignant Tumors of Larynx, Hypopharynx, Nasopharynx and Sinuses. F. D. Woodward and V. W. Archer, Charlottesville.—p. 751.  
Treatment of Nausea and Vomiting of Pregnancy with Chloretone. E. M. Ellerson, Staunton.—p. 755.  
Variability of Blood Pressure. E. A. Hines Jr., Rochester, Minn.—p. 757.  
Induction of Ovulation. W. Bickers, Richmond.—p. 760.

**West Virginia Medical Journal, Charleston****36:537-584 (Dec.) 1940**

- \*Treatment of Pernicious Vomiting of Pregnancy. F. C. Irving, Boston.—p. 537.  
Phrenico-Exeresis. F. J. Geraghty and T. B. Aycock, Baltimore.—p. 546.  
\*Arachnidism. F. C. Hodges, Huntington.—p. 550.  
Suprapubic Transvesical Repair of Vesicovaginal Fistulas. G. G. Irwin, Charleston.—p. 553.  
Treatment of Acute Deliriums. K. M. Bowman, New York.—p. 556.

**Treatment of Pernicious Vomiting of Pregnancy.**—Irving discusses the treatment of 225 consecutive patients with hyperemesis gravidarum encountered among 39,724 pregnant women admitted to the Boston Lying-In Hospital or in the outpatient department during a period of twelve years. Only 73 were patients registered for care in the clinic; the remainder were sent in as emergency cases and were generally from a higher economic stratum than those usually accepted at the clinic. Contrary to the usual opinion, 61.3 per cent of the patients had been pregnant before. This proportion agrees with the usual ratio of multigravidas, which is about 60 per cent of the total. Of the 138 muligravidas affected, 70 had vomited excessively in one or more previous pregnancies. The greatest number entered between the sixth and twelfth weeks of gestation. Contrary to the many attempts to link pernicious vomiting to preeclampsia, the author points out that not only do the two diseases occur at different periods of pregnancy but the general signs and symptoms of each in no way resemble one another; nor do the organs of fatal cases show the same changes. His patients with pernicious vomiting showed later in pregnancy no more tendency toward preeclampsia than did the others in the clinic; the ratio in their case was 1:22.5, and the general ratio 1:21. All pathologic reports show the hepatic change to be the same fatty degeneration that follows extreme starvation. The necrotic changes reported by earlier writers were not seen. A pulse rate of 110 or more always indicates a very sick patient. Peripheral neuritis is the most serious complication. Other complications are puerperal psychosis, pyelitis, pulmonary tuberculosis, hydatidiform mole, renal tuberculosis and acute appendicitis. For the mildly affected patients not requiring hospitalization, reassurance, a fat free diet rich in carbohydrates taken in small amounts six or seven times a day and a mild sedative usually suffices. For the seriously sick patient, hospital care under complete isolation from friends and family, including the husband, is necessary. The lower part of the intestine is emptied by enemas, and from 3 to 9 grains (0.2 to 0.6 Gm.) of pentobarbital sodium or any suitable barbiturate is given by rectum and repeated often enough to maintain the patient

in a somnolent condition. Opiates are avoided, as they appear to increase vomiting. A hypodermoclysis of 1,500 cc. of physiologic solution of sodium chloride is then given and sufficient daily amounts are administered to maintain fluid balance. An intravenous drip of 5 or 10 per cent dextrose is given at 30 to 40 drops a minute and repeated at from eight to twelve hours. From January 1928 to January 1934, 110 patients were treated in this manner; 6 died and 19 were subjected to therapeutic abortion. As the pathologic changes of the patients who died were those of starvation, the Levine nasal tube as a method of forced feeding was used and improvement was at once apparent. Up to January 1940, 115 patients were treated in this way with no deaths and only three therapeutic abortions. At present in addition to the described regimen the Levine tube is passed and the stomach gently washed with warm water. A half hour later a rectal drip is started. From 4 to 6 ounces (120 to 180 Gm.) of milk containing 2 heaping teaspoons of Harris yeast concentrate is given by the Levine tube, followed in an hour by 4 to 6 ounces of orange juice sweetened with Karo corn syrup and one hour later by 6 ounces of a rich eggnog made with cream and egg, and one hour later by milk and the Harris yeast concentrate. This routine is repeated until fourteen out of twenty-five hours are completed. Each feeding requires about forty minutes and is given at body temperature. Thiamine hydrochloride, ascorbic acid and liver extract are given intramuscularly. In spite of these measures there is a steadily rising pulse which remains above 110 or if the vomiting with jaundice is intractable the pregnancy should be interrupted. If twenty-four hours may be devoted to the process, the safest procedure is to pack the cervix and vagina firmly and the next day, after sufficient dilatation, to remove the ovum with a placental forceps and a dull curet. If such time cannot be taken, vaginal hysterotomy may be performed. Avertin with amylene hydrate, because of its effect on the liver, is interdicted. Sacral or low spinal anesthesia, if skilfully given, is perhaps the best of all.

**Arachnidism.**—Hodges reports the case of a woman in shock, complaining of excruciating general pains, most extreme in the back and next in the abdomen, who three hours previously, while lifting a board in the front yard, felt a sharp prick, like that of a needle, on the ring finger of her right hand. During the next two or three minutes a small white area appeared at the site of the initial pain; then her right arm began aching and the fingers of the right hand became red. Half an hour later there was aching in the right axilla and breast, following which her entire body, especially the lower part of her back, was seized with an excruciating, throbbing, aching pain with moderate headache. She became nauseated but did not vomit and noticed numbness with partial paralysis of both arms. When first seen by the author she was unable to stand alone, was perspiring freely and was in a state of apprehensive misery, pain and shock. One-fourth grain (0.015 Gm.) of morphine was injected and half an hour later, as most of the pain had disappeared, she was sent home. The following day at 2 p. m. she was reported to be much worse and was sent to the hospital, where 10 cc. of a 10 per cent solution of calcium gluconate was given intravenously. This was followed by marked relief from pain. The calcium gluconate was repeated the following morning and again gave some comfort. Feeling much improved on the afternoon of the second day, she returned to her home. She remained weak for five days, with an almost constant ache of her right arm, but complained of no discomfort in the bitten finger. Fifteen days after the bite she felt as well as ever in every respect. There was marked desquamation of the bitten finger. The premises were searched, and three black widow spiders were found. The author suggests that poisoning by the bite of a black widow spider be classified as a distinct medical entity. The frequency with which the black widow spider is found in the vicinity varies with one's interest. During a period of less than three weeks, more than twenty have been collected. The number of cases of arachnidism appears small considering the numbers and the distribution of the spider. Many unnecessary operations could be avoided if all physicians recognized that an acute condition with rigidity of the abdomen, mild fever, leukocytosis and occasionally nausea and vomiting may supervene as a result of the bite of the black widow spider.

## FOREIGN

An asterisk (\*) before a title indicates that the article is abstracted below. Single case reports and trials of new drugs are usually omitted.

## British Medical Journal, London

2:583-618 (Nov. 2) 1940

- Concentration and Drying of Plasma. F. X. Aylward, B. R. S. Mainwaring and J. F. Wilkinson.—p. 583.  
 \*Dysmenorrhea and Sterility: Personality Studies. E. Wittkower and A. T. M. Wilson.—p. 586.  
 Traumatic Chylothorax. C. J. Cellan-Jones and W. Murphy.—p. 590.  
 Common Bile Duct Obstruction: Importance of Surgical Decompression. A. N. Canonico.—p. 591.  
 Bilateral Edema of Legs and Ankles Following Fixation of Chest for Fractured Ribs. B. Hirsh and R. Ellis.—p. 593.  
 Economy in Barium Meal Examinations. F. Roberts.—p. 602.  
 Control of Lice. P. A. Buxton.—p. 603.

**Personality in Dysmenorrhea and Sterility.**—Wittkower and Wilson made biographic studies of 57 unselected patients with primary dysmenorrhea, from 16 to 40 years of age, and of 30 sterile women from 21 to 45 years of age. The study concerned itself with family background, childhood characteristics, the reactions to various phases of adolescence and the adult personality. A group of 30 primigravidae who had never suffered from dysmenorrhea served as controls. The study shows that usually patients suffering from dysmenorrhea as children had often been either unusually aggressive and boisterous tomboys resenting their feminine role or ailing complaining children unwilling or unable to give up their childish dependence on their parents and possessing strong needs or cravings for sympathy and protection. Psychologic attitudes and allied emotional states may lead to increased interest and awareness of physiologic uterine functions or/and to an autonomic endocrine disturbance affecting uterine function. In the latter instance the pain might easily arise from relative ischemia disturbing the relation between the reciprocally innervated muscular contraction of body and cervix and the vasomotor state of the organ. The sterility patients, as in the case of dysmenorrhea, were even as children different from the control group of primigravidae of the same age who in childhood were well or fairly well adjusted individuals. Psychologically well adjusted types were found in great excess in the control group and only 2 of this type were observed in the sterility and dysmenorrhea groups. As children the dysmenorrhea group showed psychologic maladjustment four times as often as the control group. Of these maladjusted types the sterile group contained a high excess of ailing, timid, unsocial children, devoid of self assertion, while the dysmenorrhea group were usually boisterous and manifestly aggressive—obstinate, bad tempered or headstrong. As adults the dysmenorrhea patients were deeply resentful of their feminine role or obviously immature physically and either shy and shut in or chronically anxious and complaining. As adults the majority of sterile patients displayed unusual self centeredness in social and personal relations, clearly seen in a sexual frigidity, with abnormal reactions to coitus.

## Lancet, London

2:507-536 (Oct. 26) 1940

- \*Blood Substitutes in Treatment of Acute Hemorrhage: Experimental Evaluation. G. A. H. Buttle, A. Kekwick and A. Schweitzer.—p. 507.  
 Nutritive Value of White Flour with Vitamin B<sub>1</sub> Added and of Wholemeal Flour. Harriette Chick.—p. 511.  
 \*Subacute Bacterial Endocarditis Treated with Sulfapyridine and Heparin. C. M. Fletcher.—p. 512.  
 Late Effects of Subdural Hemorrhage. E. A. Linell.—p. 514.  
 Axillary Embolectomy: Case. J. F. Hughes and P. Berry.—p. 516.  
 Brucella Melitensis in Cow's Milk. F. W. Duke.—p. 517.  
 Detection of Tuberculosis Among Recruits. G. G. Kayne.—p. 518.

**Blood Substitutes for Acute Hemorrhage.**—According to Buttle and his associates, storage of blood in banks has gone far to mitigate the delay involved in obtaining and bleeding donors, but, until blood can be stored for longer than a few weeks, blood banks will remain either wasteful or inadequate. There is need therefore for a blood substitute which can be stored for long periods, accumulated in large stocks and immediately available where casualties are likely to be received. The authors consider the therapeutic value of various blood substitutes. The therapeutic action of various blood substitutes has

been compared, under standard experimental conditions, with those of whole blood, and the conclusion was reached that plasma is the only one which, in the cat, consistently gives results approximate to those obtained with whole blood. The authors place the other substitute solutions in the following descending order of value: serum, hemoglobin-Ringer, gum-saline, red cells in crystalloid solution, isotonic saline and isotonic dextrose. They conclude that filtration is the best method of overcoming the danger of plasma infection.

## Sulfapyridine and Heparin for Bacterial Endocarditis.

—Fletcher suggests that the encouraging results reported by Kelson and White in the treatment of subacute bacterial endocarditis with sulfapyridine and heparinization of the blood may lead to its further trial. The object of heparinization is to restrict further thrombotic deposition on the cardiac valves and to diminish the nidus and culture medium for bacterial growth, to prevent embolism from the freeing of fresh thrombus, and to check the growth of vegetations so that proliferating fibroblasts may fill in the area thus limited. At the same time, and for a week before and after the fourteen days of heparinization, sulfapyridine is given for its bacteriostatic action. The author describes a case of subacute bacterial endocarditis in which treatment with sulfapyridine and heparin was attempted, but the patient died from cerebral hemorrhage. To render the blood less coagulable in a disease in which emboli are common is to run the risk of serious hemorrhage. In many cases of infective endocarditis, however, administration of sulfapyridine temporarily sterilizes the blood stream and abolishes embolic accidents. Thus the week of therapy by sulfapyridine before starting the heparin acts as a safeguard against serious hemorrhage. In the reported case this safeguard failed, for a positive blood culture persisted and petechiae continued to appear while sulfapyridine was being given. Three other cases have been reported in which hemorrhage occurred during heparin treatment. Of the five other patients so far reported (all by Kelson and White) to have survived heparin treatment, only one had a positive blood culture at the beginning of the heparinization. In this case no improvement was obtained. The conclusion suggested by this small series is that the persistence of a positive blood culture, and in particular the continued appearance of embolic phenomena, should contraindicate heparin treatment. Swain, using *in vitro* tests in support of clinical observations, demonstrated that some strains of *Streptococcus viridans* are susceptible to sulfapyridine, while others are unaffected. He suggests that heparin treatment should be undertaken only when such tests show that the infecting strain of *Streptococcus viridans* is amenable to chemotherapy.

## Medical Journal of Australia, Sydney

2:395-422 (Oct. 26) 1940

- Sternal Puncture. J. A. McLean.—p. 395.  
 \*Argentaffin Carcinomas ("Carcinoids") of Small Intestine. R. A. Willis.—p. 400.  
 Schick Reaction: Stabilized Toxin Compared with Toxin Diluted in Saline Solution. H. Wilson and N. E. Goldsworthy.—p. 403.  
 Some Surgical Pancreatic Diseases. T. M. Furber.—p. 405.

## Argentaffin Carcinomas of Small Intestine.—Willis cites

6 cases of argentaffin carcinomas of the small intestine encountered during the last three years at the Alfred Hospital. Metastases developed in 4; in 2 it was widely disseminated blood-borne metastases which occasioned serious diagnostic errors. In another case a small primary growth was accompanied by a large, probably metastatic, growth in one kidney. The observations emphasize the fact that these tumors are highly malignant and show the falsity of the implication of innocence in Oberndorfer's name "carcinoid" tumor; the tumors are frank carcinomas, sometimes extremely malignant. In all 4 cases in which there were metastases the author observed that very small, often symptomless, primary tumors may produce bulky, clinically obtrusive metastases. Unless the intestine is opened and carefully examined at necropsy, the primary intestinal growths in many cases may easily escape discovery. He considers it possible that tumors found in the pancreas, biliary tract or stomach of subjects with multiple intestinal growths may not be metastases but multiple primary formations.



## Presse Médicale, Paris

48:601-616 (July 24-27) 1940

- \*Resection of Aortic-Iliac Bifurcation with Bilateral Lumbar Sympathectomy in Thrombosis of the Aorta: Syndrome of Obliteration of Terminal Portion of Aorta Due to Arteritis. R. Leriche.—p. 601.  
Clinical Study of Maladies in Melinite Factories. F. Trémolières, R. Goiffon and P.-E. Robert.—p. 604.

**Resection of Aortic-Iliac Bifurcation in Aortic Thrombosis.**—Leriche discusses the syndrome of aortic occlusion due to thrombosis and the bilateral lumbar sympathectomy that was combined with the resection. The pathologic process is characterized by five symptoms: loss of penile erection, which may have existed for a long time; extreme lassitude and fatigability of both lower extremities; complete atrophy of both lower extremities, nearly always present; pallor of the skin of the feet and legs, even in standing position, and assuming an ivory or marble appearance when the leg is raised, and absence of pulse in the leg and the femur. Neither the skin nor the nails indicate nutritional dysfunction. The toes have a good appearance. In the terminal phase there are found cyanosis of the feet and legs, desquamation of the skin, ulcer formations at pressure points, preceded by ecchymosis, and gangrene, accompanied by extreme pain. The diagnosis can be confirmed by arteriography. Leriche regards resection of the involved segment of the aorta and of the iliac arteries combined with bilateral lumbar sympathectomy as the ideal treatment. He reports two carefully documented cases. In the first case the bilateral section involving the first lumbar ganglion was observed three and one half years later to have given good results. Here the occlusion amounted to from 2 to 3 cc. and was situated somewhat above the bifurcation. The patient (35 years old) was able to rise on the third day and was discharged on the tenth day. Blood pressure fell from 160 systolic and 110 diastolic to 120 systolic and 90 diastolic. The second patient, aged 61 years, was first seen when gangrene had already set in. The right foot and leg could be saved by the operation. The left foot was too far gone to be salvaged. No later observations could be made of the patient as he was lost sight of in the Strasbourg evacuation. The author believes that arterial thrombosis in the terminal section of the aorta above the inferior mesenteric artery occurs more frequently than is generally assumed. Diagnosis, which should be easy because of the clear symptoms and the slow evolution of the disease, frequently is at fault because of professional reluctance to accept the view that aortic thrombosis with bilateral iliac involvements can exist without mortification in the legs and feet. The delay in surgical intervention, however, due to hesitating or incorrect diagnosis, may necessitate partial amputation or induce a fatal termination with agonizing pains. He believes that aortic occlusion with simultaneous secondary involvement of the iliac arteries is the usual thing and not primary iliac occlusion without involvement of the aorta.

48:665-680 (Aug. 21-24) 1940

- Role of the Kidneys in Tests for Induced Galactosuria. M. Chiray, H. Maschas and J. Germond.—p. 665.  
\*Treatment of Painful Amputated Stumps. E.-P. Leclerc.—p. 667.  
Microdetermination in Serodiagnosis of Syphilis. R. Demanche.—p. 669.

**Pain in Amputated Stumps.**—Leclerc employed procaine hydrochloride, simple nerve resection and lumbar sympathectomy in treating pain in amputated stumps. Procaine hydrochloride, though only rarely affording permanent relief, is regarded by the author as valuable in indicating further therapy. For amputations of recent date and with localized pain, procaine hydrochloride gives good temporary results. In old and aggravated cases, in which the drug was unable to prevent recurrence of pain, satisfactory results were obtained by lumbar sympathectomy for the lower extremity and by ablation of the stellate ganglion for the upper extremity. In the mixed type of stump pains in which the remaining stump as well as the removed anatomic portion due to hyperesthesia was involved, favorable analgesic action of the drug indicated resection of the sympathetic chain and ganglions. If this operation was ineffective, a simple nerve resection followed by prompt suture or grafting did the job. This supplementary operation was not often necessary. An adequate interval of time, however, must then be allowed not only to avoid further damage to the patient but to gauge the efficacy of the first

operation. Lumbar sympathectomy, performed by the author in a limited number of cases, achieved remarkable results in relieving formication and vasomotor disorders. The author cites a remarkable case in which multiple operations had been performed for frozen feet since 1917. Seen in 1935, the patient was suffering agonizing pain. The stump indicated vasomotor and trophic dysfunction and presented a neuroma at the site of the cicatrix. Lumbar sympathectomy was done and all pain ceased on the evening of the same day, not to recur. Seen in 1939, the patient was well and had qualified as a game-keeper, though before that he had been unable to endure any artificial apparatus. The author obtained better results by resection of the sympathetic chain and ganglions, done either as the first operation or in order to correct unsatisfactory previous results, than by all other therapeutic procedures, especially in the thoroughness with which the whole clinical picture was altered. This operation was the operation of choice whenever procaine hydrochloride was observed to alleviate pain. Simple nerve section for control of imaginary nostalgic pain in the severed limb, followed by prompt nerve reconstitution after using phenol at the central termination, was tried and abandoned for the method of choice. Periarterial sympathectomy, with the exception of 1 case, yielded only temporary relief. Early intervention offers the best result.

## Gior. d. r. Accad. di Med. di Torino, Turin

103:37-122 (April-June) 1940. Partial Index

- Sulfanilamide in Pneumonia. A. Allodi.—p. 80.  
\*Sulfanilamide in Herpes Zoster. G. Roasenda.—p. 112.

**Sulfanilamide in Herpes Zoster.**—Roasenda obtained satisfactory results with sulfanilamide in 3 cases of subacute and severe herpes zoster. The drug was administered in doses of 0.3 Gm. each three times a day in subacute cases, and at intervals of six hours in severe cases, for the first three days. Following this, two tablets of the same dose were given twice a day for a week. The patients received analgesic drugs for the control of pain and a mild hypnotic drug at retiring. In all cases pain abated, the spread of the lesions was arrested and fever abated and disappeared within the first three days of the treatment. The cutaneous lesions healed within the first week of the treatment even in cases of severe herpes with extensive lesions of gangrenous character.

## Archivos de Pediatria del Uruguay, Montevideo

11:685-754 (Sept.) 1940. Partial Index

- \*Electrocardiogram in Diphtheria. M. R. Arana and R. Kreutzer.—p. 685.

Newly Born Infants and Nurslings. R. B. Yannicelli.—p. 705.

**Electrocardiograms in Diphtheria.**—Arana and Kreutzer report electrocardiographic studies on 621 children with diphtheria. Serious abnormalities of the first and second degrees were revealed in 257 cases, and moderate abnormalities in 321. Recovery from diphtheria took place in 42 of 43 patients with a normal heart, in 67 of 162 and in 79 of 95 patients with important electrocardiographic abnormalities of the first and second degrees respectively, and in 295 of 321 patients with moderate electrocardiographic abnormalities. The electrocardiogram became normal in 7 of 26 and in 8 of 16 patients with important abnormalities of the first and second degree and in 11 of 19 patients with moderate abnormalities. The observations were followed for from one to four years. Permanent electrocardiographic abnormalities of the first and second degree remained unchanged in 19 of the 26 and in 8 of 16 patients of the first and second groups, respectively, while permanent heart sequels of minor importance remained in 8 of the 19 patients of the third group. Observations were continued for less than three months in 41 cases of 67 and in 63 of 79 recovered patients of the first and second groups, and in 276 of the 295 recovered patients of the third group. The electrocardiograms exhibited a tendency to become normal in cases of mild heart lesions. There were 95 deaths among 162 cases, and 16 among 95 cases of the first and second groups, respectively, and 26 among 321 cases of the third group. The authors emphasize the importance of serial electrocardiograms in diphtheria. The disease may cause transient or permanent heart disease with electrocardio-

graphic abnormalities of any type. Certain types of diphtheritic heart disease are revealed by electrocardiography and not by clinical symptoms. Electrocardiograms have a prognostic significance. A normal heart indicates good prognosis except in malignant diphtheria. The milder the electrocardiographic alterations the better the outlook for recovery from diphtheria, and the more frequent the normalization of the electrocardiogram after recovery. The need of making electrocardiograms of patients before discharging them is obvious.

### Prensa Médica Argentina, Buenos Aires

27:2187-2240 (Oct. 23) 1940. Partial Index

\*Bilateral Spontaneous Pneumothorax. M. R. Castex and E. S. Mazzei.—p. 2187.

Arthritis Deformans of Knee Joint. A. A. Covaro.—p. 2203.

**Bilateral Spontaneous Pneumothorax.**—Castex and Mazzei review the literature on spontaneous bilateral pneumothorax and report a case of their own. Bilateral spontaneous pneumothorax is rare. It is not necessarily fatal. It occurs in adults, especially men. It may take place simultaneously in the two pleural cavities or several days or weeks apart. In either case the acuteness and the evolution of the condition depend on the pathogenic type of the pneumothorax which can be ascertained by the roentgen examination of the lung and pleuroscopy. The cicatricial, tuberculous and emphysematous pneumothoraces are the most frequent types. The so-called idiopathic pneumothorax which is cicatricial and is caused by rupture of air blebs in the subpleural cicatricial tissue is benign. The cicatricial pneumothorax from perforation of a scar of sclerotic pulmonary tissue follows a long evolution without fever and pleurisy. Frequently it causes moderate dyspnea because of intrapleural hypertension on one side. It is capable of improvement and of healing of the perforation with disappearance of the pneumothorax. Tuberculous and emphysematous pneumothoraces are serious. The prognosis must be cautious because of the ensuing cardiac and respiratory insufficiency. The treatment is symptomatic and is directed toward the control of the cough, dyspnea and pain. It consists in rest and of measures for the prevention of the cardiac and respiratory insufficiency. Oxygen therapy and removal of intrapleural air are indicated. In the case reported by the authors the perforation of a scar of sclerotic pulmonary tissue was visualized by pleuroscopy and was reproduced by pleurophotographs. It increased during inspiration. The patient was put on rest with symptomatic treatment. The intrapleural air was removed in amounts of from 800 to 3,000 cc. at each treatment at weekly intervals for about three months. The perforation healed spontaneously and the pneumothorax was absorbed.

### Fortschritte der Therapie, Leipzig

16:227-266 (July) 1940

Multiple Sclerosis and Its Treatment. G. Voss.—p. 227.

\*Chemotherapeutic Use of Methenamine in Virus Diseases. K.-H. Jaeger.—p. 231.

Blood Transfusion Utilizing a Modified Form of Heparin and an Infusor. J. Clemens.—p. 235.

Meningococcic Meningitis Treated with Meningococcus Serum and Sulfonamides. G. Perkuhn and H. E. Büttner.—p. 251.

Pertussis and Its Treatment. H. Lentze.—p. 254.

**Methenamine in Virus Diseases.**—Jaeger reports on the therapeutic effects of methenamine in herpes, erythema and varicella. The drug, given orally and by injection in relatively large daily doses totaling at least 6 to 8 Gm. in adults, was able to heal rapidly different types of herpes, such as herpes zoster and simplex. Cases of herpes simplex, with few exceptions, yielded at once to medication, irrespective of their site or etiology, whether due to infection, digestive disorders or the menstrual cycle. The drug was no less effective in erythema multiforme and erythema nodosum. In twenty cases of chickenpox the course of the disease was abbreviated and the appearance of the rash prevented in others. Mild hematuria that occasionally occurred under the impact of heavy doses could be promptly checked through discontinuation of the drug without sequels. The results observed led the author to assume that herpetic disorders owe their origin to the same cause as the varicellae whether this is a bacterial incitant or a substance; the clinical picture, however, in each case is determined by modifying factors. There may exist also a connection between

herpetic diseases and the erythemas just mentioned. The specific therapeutic and prophylactic effects on varicella are due to the molecular action of the drug as a whole.

### Khirurgiya, Moscow

1-160 (No. 8) 1939. Partial Index

\*Intra-Arterial Blood Transfusion in Shock, Agony and Arrested Heart. I. A. Birillo.—p. 3.

Acidity of a Wound Irrigated with Solution of Iodine in Alcohol. V. V. Moscalenko.—p. 18.

Biochemical Changes in Muscles in Treatment of Fractures with Eggshell Preparations. G. A. Dudkevich.—p. 24.

Traumatic Lesions of Gastrointestinal Tract. V. D. Goloranov.—p. 29.

Operative Intra-Abdominal Interventions to Counteract Pain. N. N. Nazarov.—p. 37.

Local Anesthesia According to Vishnevskiy for Perforated Gastroduodenal Ulcers. S. I. Voronichkin.—p. 43.

**Intra-Arterial Blood Transfusion.**—Birillo bled dogs to the extent varying from 69.7 to 88 per cent of the total blood volume. One minute after the complete arrest of the heart action and one-half minute after the cessation of respiration he began intra-arterial transfusion of fresh citrated blood. From 250 to 600 cc. was injected into the right carotid artery in the direction of the heart by means of a Riva-Rocci blood pressure apparatus combined with that of Bobrov. Epinephrine in the amount of 1 cc. of a 1:1,000 solution was also injected by piercing the connecting rubber tube with a fine needle attached to a syringe. Heart contractions commenced at once and the blood pressure began to rise after the introduction of the first 25 to 50 cc. of blood. Respirations returned soon after the reactivation of the heart. All eleven dogs survived the experiment. The author practiced intra-arterial blood transfusion from one-half to one minute after cessation of heart action induced by chloroform narcosis. Following the transfusion the author bled the dog by way of one or both jugular veins in order to relieve the right side of the heart. All the dogs were resuscitated. The success of the experiment depended, in the author's opinion, on the fact that blood and epinephrine found their way immediately into the coronary arteries and the general arterial tree. Next, the author experimented with a series of 9 dogs in a state of shock with blood pressure varying from 60 mm. of mercury to 0. Intra-arterial injections of citrated blood in the amounts of from 250 to 380 cc. revived all the animals. In another series of 9 dogs a similar experiment was carried out, the intravenous route being substituted for the transfusion of blood with epinephrine. All the animals perished except 2, in which the author resorted, after failure with the intravenous method, to intra-arterial transfusion. Birillo applied the method to 4 clinical patients in the agonal state and was able to revive them for four to twenty-four hours. Citrated blood was introduced into either the ulnar or the radial artery. All the patients died, however, because of destructive and irreversible lesions in vital organs. The author believes that the method of intra-arterial blood transfusion may find application in patients dying of some acute process but possessing a normal cardiovascular system. Active bleeding constitutes a contraindication.

### Nordisk Medicin, Gothenburg

7:1527-1566 (Sept. 14) 1940. Partial Index

#### Norsk Magasin for Lægevidenskaben

\*Cause, Treatment and Prevention of Tendency to Bleeding in Newborn. K. K. Nygaard.—p. 1535.

Case of Synovialoma in Hip Joint Region. E. Schie.—p. 1538.

Acute Encephalitis—Especially Prognosis. K. Motzfeldt.—p. 1541.

**Bleeding in Newborn.**—Nygaard considers inactivity of the intestinal flora in the newborn as probably only one of the factors concerned in the transitory hypoprothrombinemia which develops in the first days after birth. He is inclined to believe that vitamin K has its greatest possibility not in therapy but in prophylaxis of the tendency to bleeding which occurs when the prothrombin reaches a certain low level and says that the most satisfactory results seem to be attained by the administration of vitamin K to the mother before birth. With the synthetic preparation 2-methyl-1:4-naphthokinon a dose of 1 tablet (10 mg.) daily may be given for one or two weeks before birth; as a rule the dose must apparently be increased the more immediately before birth the vitamin is given. He noted no toxic symptoms in mother or child.

## Book Notices

**Organization, Strategy and Tactics of the Army Medical Services in War.** By Lieut.-Colonel T. B. Nicholls, M.B., Ch.B., Medical Officer, A. R. P. Derbyshire County. With Chapters by Air-Commodore A. S. Glynn, M.B., Ch.B., K.H.S., Fighter Command, R. A. F., Colonel A. R. Laurie, M.B., Ch.B., D.M.R.E.(T.A.), 2nd Anti-Aircraft Division, and Colonel F. G. Lescher, M.C., M.A., M.D., Group Officer, E. M. S. Second edition. Cloth. Price, \$5. Pp. 488. Baltimore: Williams & Wilkins Company; London: Baillière, Tindall & Cox, 1940.

The medical service in war is a large organization which has the duties not only of treating the wounded and sick but of providing for them food, clothing, warmth, discipline, pay and transportation of enormous numbers. Medical skill is required to keep the troops fit and healthy, and a high degree of administrative ability is necessary to supply and coordinate the various forms of transport—ambulances, stretcher bearers, trains, ships, barges—and to provide vast quantities of dressings, drugs, instruments, splints and all sorts of appliances. In the last World War, some eleven million sick and wounded from all parts of the world suffered from every conceivable injury and sickness. This tremendous duty was performed so well that 75 per cent of these eleven million sufferers were restored to their health and duties. The author, a retired officer of the Royal Army Medical Corps, during the World War commanded almost every kind of medical unit in the field on active service. His book is based on wide personal experience and on five years of labor since then performed to provide a book which deals with every problem that a medical officer in the field may have to solve. Heretofore British medical officers had to study many books of reference, while some necessary information could not be obtained from any printed source. The author has brought this information together in one volume. The fact that a second edition was necessary in less than four years indicates that the book is serving its purpose. The general organization of the medical services and the constitution of the medical units are those of the British army. Nevertheless, the general principles of those considerations, as well as those of strategy and tactics, are similar in all large military medical services. In addition to questions of supply and tables of organization are instructions about how to maintain supplies in quantity and in good condition; also discussions of personnel and organization of general hospitals, base hospitals, hospital trains, hospital ships, antiaircraft medical services, transport of casualties by air, collecting post, dressing stations and regimental units. There is also a series of tactical problems and exercises for study in connection with examinations for promotion. The book covers a wide scope and fills a long-felt need.

**The Surgery of the Alimentary Tract.** By Sir Hugh Devine, M.S., F.R.A.C.S., F.A.C.S., President, Royal Australasian College of Surgeons, Melbourne. Cloth. Price, \$15. Pp. 1,046, with 690 illustrations. Baltimore: William Wood & Company, 1940.

Surgery of the alimentary tract is a modern development. Its span is not more than a half century and many of the more recent procedures have not received proper evaluation. The inherent difficulty in the diagnosis of gastrointestinal lesions is reflected by a similar difficulty in assessing the surgical treatment. As the author states, the ability to evaluate the symptoms and signs presented by the patient is a full responsibility of every surgeon professing to treat gastrointestinal diseases. Further, a study of the history of alimentary tract diseases reveals that the greatest contributions to their diagnosis and correlation with pathologic changes must be credited to the science of surgery. It is proper, therefore, for any comprehensive surgical work to include discussion of what is ordinarily considered "medical" gastro-enterology.

In light of this the author begins with a discussion of the dyspepsias. One who has had as much experience as Devine no doubt has accumulated considerable wisdom and insight, inexpressible as these might be, regarding that vague entity dyspepsia. Accordingly he has divided the dyspepsias into two groups, medical and surgical. One of the more important distinctions between these is pain. Almost immediately, however, exceptions to this rule are made. Such a separation is a dangerous concept. Dyspepsia, or indigestion, especially in the elderly, is an important signal

not to be lightly disregarded. Investigation and not contemplation is indicated as soon as possible. Medical dyspepsia, or functional indigestion, should always be a diagnosis made with reservations. The author proceeds to illustrate this fact aptly, although he has not emphasized it sufficiently. However, the various dyspepsias (better dyspeptic symptoms) associated with organic diseases are well presented. Diagnostic efforts such as x-ray examination and gastroscopy are discussed sufficiently for the surgeon. The diagnosis of appendical dyspepsia by roentgenologic methods is not widely accepted in this country.

The portrayal of surgical procedures is extremely interesting. The author relies on a number of mechanical aids and self-retaining retractors. While in his hands undoubtedly these work well, in this country well equipped hospitals with enough trained assistants are available for private as well as public patients. Of course, the Devine exclusion operation is presented. Any surgeon, however, who undertakes to treat peptic ulcer by excluding rather than removing the pylorus and antrum assumes a grave responsibility. Especially good are the sections on hydatid disease, with which the Australians have much more experience. Other topics dealt with are biliary diseases, appendicitis, intestinal obstruction and other intestinal diseases amenable to surgical treatment. These subjects are presented uniformly well. No mention is made of the use of vitamin K in the prevention and treatment of hemorrhage in the presence of jaundice. The problem of fluid balance and decompression in intestinal obstruction is not adequately discussed. This is important, because in spite of the newer methods of treatment great reduction in mortality has not resulted. The illustrations are good, and in spite of some serious omissions the text represents much that is good common sense. The surgeon concerned with diseases of the alimentary tract can profit by perusal of this volume.

**La sénescence et le rajeunissement.** Par le Docteur Paul Nlehangs, chirurgien et urologue F. M. H. à la Clinique de Clarens et aux hôpitaux de Vevey et de Montreux (Suisse). Traduction libre de l'allemand. Paper. Pp. 72. Paris: Vigot Frères, 1937.

The author discusses senescence and rejuvenation and goes into details on how to avoid the former and effect the latter. He analyzes the problem of senescence, of extinction of life and of final death. He recalls that growth and maturity, cicatrization, cure and regeneration, even sensation and perception, are manifestations of cellular interactivity. Senescence begins in the cell and ends in death, which is nothing else but the disintegration of the edifice formed by the cells. Protozoans know neither old age nor death. Under suitable surroundings they are capable of indefinite reproduction. Each individual protozoan achieves its existence by fission. Metazoa know neither senescence nor death. The life of certain of these organisms may be without limit (jellyfish, corals, hydras and hydroid polyps). Certain cells can survive the death of the organism for long periods. Thus a mouse may live for two months, but the cells of its tegument or of one of its organs can continue to live ten years or more, if placed in a favorable culture medium (Carrel). Physiologic senescence begins in the human female at the menopause. Graafian follicles cease to rupture and the organism does not receive its monthly supply of follicular hormones. In man senescence begins in the fifth decade of life. The testicles become smaller. Endocrinologists attribute old age to secretory disturbances of the sexual glands. Stock raisers know that castration shortens life. Other endocrine glands, like the testes, also have their epoch of activity and of decline. The testicle, like the pancreas, is a double gland. Leydig, Sertoli and Steinach's F cells are discussed at length. "Is it possible to retard senescence?" the author asks and replies that the answer lies in the different measures employed to effect rejuvenation. He then gives a long list of methods that are now in use, hygienic, dietetic, organotherapeutic. He describes various operative measures that have been employed and compares their degree of efficacy, including albugenectomy—linear, cruciform and circular. Albugenectomy develops Leydig cells and not the Sertoli cells, which are more specific for rejuvenation, he points out. Transplantation of the various glands—anterior lobe of the hypophysis, thymus, thyroid, the cortex of the adrenals, of the placenta, of the sexual glands—is also described. In the lower animals, it is claimed, transplantation of the sexual

glands increases wool production, prolongs life and rejuvenates reproducing bulls and bucks. The author describes the Steinach technics and quotes Steinach's belief that the processes of cellular senescence are reversible, within certain limits, by hormonal impulsion.

**A Treatise on Medicolegal Ophthalmology.** By Albert C. Snell, M.D., Ophthalmologist, Park Avenue Hospital, Rochester, New York. Cloth. Price, \$6. Pp. 312, with 15 illustrations. St. Louis: C. V. Mosby Company, 1940.

This is the first American textbook devoted to forensic ophthalmology, although thirty-eight years ago Würdemann translated and published a book on Visual Economics. The first part of the book contains some essential principles of medical jurisprudence, stripped of their legal verbiage and stated in terms that can be comprehended by the medical man. It is commended most earnestly not only to the ophthalmologist but to all practitioners of the art of medicine as well. A careful study of the first ninety-five pages can save future legal embarrassment. The second part is given to the evaluation of visual disabilities and analyses of the basic principles involved in the act of seeing. Not only is there a careful psychologic study of visual acuity and all that it implies but there is also an equally careful study of the fractional parts of vision, as the visual field, muscle function and coordinate action. This is good reading for every ophthalmologist, whether or not he ever has to appear in court or before a compensation board. Mathematical evaluations which were prepared with the help of Mr. Scott Sterling are reduced to their simplest terms, so that a knowledge of higher mathematics is not essential. The third part deals with the practical application of the visual efficiency computation to medicolegal practice, with particular emphasis on the evaluation of visual disabilities. The author is chairman of the committee of the Section on Ophthalmology of the American Medical Association on compensation for eye injuries. The report of this committee, which was adopted some fourteen years ago, is now undergoing revision and will be presented at the 1941 session of the Association. The whys and wherefores of the report and its revision are explained in great detail in the last pages. This book is a real necessity for every modern ophthalmologist.

**Child Psychology for Professional Workers.** By Florence M. Teagarden, Ph.D., Professor of Psychology, University of Pittsburgh, Pittsburgh. Cloth. Price, \$3.25. Pp. 641, with 8 illustrations. New York: Prentice-Hall, Inc., 1940.

While there have been many other textbooks written on the subject of child psychology, this is the first definitely directed toward aiding the social worker, physician and psychiatrist in evaluating the various points of information given in taking a history in a problem case. While most of the information given in the book describes the behavior of normal children, there is enough of the description of behavior problems and pathologic youngsters, and those having emotional conflicts, to be greatly revealing. The amount of systematic material collected between two covers which could be used to aid the social worker in finding out the meaning of the various traits has been extremely limited. While every trained worker in the field and, of course, the trained pediatrician and child psychiatrist have learned by bitter experience or perusal of the literature what the effect, for instance, of crippling might be, there has been no other treatise which covers not only the mental result of crippling but what also must be expected of the normal noncrippled child at the same developmental level. The book is so all inclusive that it is impossible to give a complete summary of the contents, but parts of it must be stressed. First, the book begins with a sensible discussion of the meaning of heredity as far as child development is concerned. The next chapters deal with infancy, the preschool child and the usual physical habits found in these children, including toilet habits and difficulties encountered in toilet training. The child in its home and away from home is discussed from the point of view of the emotional meanings of the home and the foster home. There is also a complete chapter on adoption which covers the subject in a comprehensive and simple way. The child's emotions, sex life, intelligence, school reactions and behavior difficulties are all made the subjects of chapters. Most important to the physician is the chapter on the psychologic and social problems incident to diseases of childhood. The author,

to complete her volume, included chapters dealing with the auditory and visual handicaps and speech defects which perhaps bring children most often to the physician. The pediatrician must of necessity profit by a book of this sort, for it will spare him the effort of going through a mass of uncorrelated literature to aid him in supplementing his own knowledge of specific subjects. There are comprehensive bibliographies at the chapter ends. All in all, the book is excellent. While much of the discussion of problem material rests on a hypothetical basis, the hypothesis is usually the one most accepted by psychiatrists and orthopsychiatrists, although the author herself is a psychologist.

**"Breathing Machines" and Their Use in Treatment: Report of the Respirators (Poliomyelitis) Committee.** Medical Research Council, Special Report Series, No. 237. Paper. Price, 60 cents; 2s. Pp. 90, with illustrations. New York: British Library of Information; London: His Majesty's Stationery Office, 1940.

A description (nineteen pages) of the various types of respirators now available in Great Britain is followed by a discussion of the clinical experience (sixteen pages) in their use. The incidence of respiratory paralysis from all causes in Britain is given some attention and is followed by a treatise on indications for use of the machines, with their management and the nursing technic involved. The choice and location of apparatus have a place in the report but necessarily are applicable only to Great Britain. The conclusions are especially well written. The authors emphasize that the machines are needed only for prolonged administration of artificial respiration and that they in no way displace the use of manual methods for emergency rescue work. It is suggested that machines be placed strategically in hospitals and the patients brought there, rather than to have the machines taken to the patients. The appendix contains twenty pages of tables showing where machines have been used, the cause of the respiratory failure, and the outcome of the treatment.

American readers are naturally most interested in what we may apply from this study to our own problem. Since this report appeared, the National Foundation for Infantile Paralysis, 120 Broadway, New York, has issued two pamphlets, one by Dr. J. L. Wilson of Detroit, giving probably the best discussion which has yet appeared on the use of respirators and the care of the patient, and a second showing the location of the respirators in the United States. The greater density of population and the smaller distances in England, as compared with the United States, make the British respirator problem quite different from ours. It is doubtful whether that phase of their study will help us, but their analyses of cases of diphtheria and poliomyelitis treated are informative. Although we have far more data from which to draw, we have made no such analyses of our cases treated.

**Holt's Diseases of Infancy and Childhood: A Textbook for the Use of Students and Practitioners.** By the late L. Emmett Holt, M.D., and John Howland, M.D. Revised by L. Emmett Holt Jr., M.D., Associate Professor of Pediatrics, Johns Hopkins University, Baltimore, and Rustin McIntosh, M.D., Carpenter Professor of Pediatrics, Columbia University, New York. Eleventh edition. Cloth. Price, \$10. Pp. 1,421, with 262 illustrations. New York & London: D. Appleton-Century Company, Inc., 1940.

The last previous edition was published in 1934. The present edition appears with a long list of collaborators and represents great changes from the original textbook by Holt or even the revision by Howland. In the present edition, large parts have been entirely rewritten. The entire section devoted to diseases of the eye has been added. Much new material appears on the endocrine disorders. There have also been extensive changes in the discussions of many diseases. Most of the collaborators are from the faculties of Johns Hopkins University School of Medicine and from Columbia University, but there are also some contributions by physicians from other schools. The bibliographies have been brought up to the present. The authors have taken advantage of many of the studies promoted through governmental agencies. The chapters on the use of the sulfonamide derivatives in children give proper consideration to the question of dosages of these agents. Typical of the up-to-date character of the revision is the late material concerning vitamin K and the so-called vitamin P. Altogether, the work on this volume has been so thorough that it may be recommended not only as a textbook for students but also as a constant desk reference for the practicing physician.

**How Life Began: A Speculative Study in Modern Biology.** By David Forsyth, M.D., D.Sc., F.R.C.P., Consulting Physician, Charing Cross Hospital, London. Cloth. Price, 5s. Pp. 106. London: William Heinemann, Ltd., 1939.

The author calls this a speculative study in modern biology. It is that and more in that it attempts to answer the age old query "Why is man?" rather than give information on "What is man?" Beginning with the biology of man, the book discusses heredity and environment. It does not advance solid arguments for one to the detriment of the other but shows how the two are related. The author shows further that the two cannot be kept in separate compartments but must be invoked together. He speaks of an "inherited environment" and shows further that the two overlap "spatially and structurally" to such an extent that it is quite impracticable to decide where one "leaves off and the other begins." The book is thought provoking, makes excellent reading and will interest the physician and those of his patients who possess a sufficient background of knowledge in biology.

**The Neuroses in War.** By Several Authors under the Editorship of Emanuel Miller, M.A., M.R.C.P., D.P.M. With a concluding chapter by H. Crichton-Miller, M.D., F.R.C.P. Cloth. Price, \$2.50. Pp. 250. New York: Macmillan Company, 1940.

British neurology of the last war was subjected to some criticism in this country for not having taken full advantage of the opportunities presented to study the so-called functional nervous disorders. Without considering the justice of that criticism, this book demonstrates that in this conflict much thought has already been given to the subject of war-caused or war-precipitated neuroses and that the British medical services are prepared to give better service and more careful study to the subject than was done in the last war. There are twelve contributors to this book. One of them, unnamed, is a staff officer attached to the Royal Army Medical Corps. The discussions in general show careful preparation and constitute good reviews of the present status of knowledge in the field. Unfortunately it appears that an extensive opportunity will be given to expand the knowledge of the war neuroses in the civil as well as the military population. The book deserves careful study in this country both for the light which it can shed on the war neuroses and for the assistance which it can offer in civil life and possibly in the work of the draft boards.

**Essentials of College Chemistry.** By G. H. Whiteford, Ph.D., Professor of Chemistry, and R. G. Coffin, M.S., Associate Professor of Chemistry, Colorado State College, Fort Collins, Colorado. Second edition. Cloth. Price, \$4. Pp. 534, with 32 illustrations. St. Louis: C. V. Mosby Company, 1939.

The first edition of this volume was reviewed in *THE JOURNAL*, Jan. 29, 1938. Many sections of the present edition have been revised and a new brief chapter on some carbon compounds essential to life processes has been added. The authors have continued the presentation of the fundamentals of chemistry in a style which is clear but necessarily limited. An interesting feature of the new edition—one of great value to the beginning student—is the inclusion of a few pertinent references to modern books and periodical chemical literature at the end of many of the chapters. These references direct the student's attention to more complete reviews of the subjects covered generally in the text. Thus they serve to stimulate, interest and acquaint the student with the useful habit of perusing the current literature as an aid to success in his chosen field of effort. Another feature of this edition is the faint green tint of the lightly glazed paper on which it is printed. The publishers have thus directly attempted to aid the reduction of eye fatigue in those students who find it necessary to read the text intensively.

**Pathological Conferences Held at the Cook County Hospital.** By Dr. R. H. Jaffé. Edited by Chester C. Guy, M.D. Cloth. Price, \$3.50. Pp. 1,164. Chicago: Cook County Hospital Internes' Alumni Association, 1940.

This is a memorial volume which preserves from oblivion a portion of Dr. Richard H. Jaffé's contributions to clinical pathology which otherwise would be lost. The titles of 119 articles on various subjects represent his more formal contributions to the science of medicine. The volume comprises 596 cases presented at the weekly pathologic conferences of Cook County Hospital during the decade 1928-1937. A summary of

the history of each patient is given and then the clinical and laboratory data followed by the results of the necropsy and comments. This method of approach presents two views of each disease—binocular vision, so to speak. The cases presented range from such unusual conditions as Hodgkin's disease of the brain, Ayerza's disease and Cushing's syndrome to a wide assortment of the more common clinical conditions. If this collection includes all those used for teaching purposes in the conferences, the solitary case of typhoid is eloquent proof of the altered occurrence of that disease since the days when the reviewer attended necropsies in Cook County Hospital. More than 200 of the cases represent leukemic and neoplastic diseases. The arrangement of the index both for diseases and for organs adds to its usefulness. Detailed minutiae of technical and morphologic considerations are omitted from the analyses in general. The pertinent facts and discussions are presented concisely. One reads with admiration the briefly detailed description of a primary malignant glomus tumor of the omentum and the elucidation of the origin and significance of glomera. The printed page does not adequately transmit personality; yet even so, those who knew Dr. Jaffé as a teacher and demonstrator of pathology will find his personal characteristics as well as his comprehensive knowledge reflected here.

**A Textbook of Anatomy and Physiology.** By Jesse Feirring Williams, M.D., Sc.D., Professor of Physical Education, Teachers College, Columbia University, New York City. Sixth edition. Cloth. Price, \$2.75. Pp. 607, with 367 illustrations. Philadelphia & London: W. B. Saunders Company, 1939.

This book has been revised, and more illustrations have been added. It departs from the usual method of presenting anatomy separate from physiology. It is intended for students in nursing schools and professional students in various fields of education, especially physical education. The suggestions on how to study as well as the practical exercises and questions given at the end of each chapter should prove valuable to the student.

**Statistical Methods Applied to Experiments in Agriculture and Biology.** By George W. Snedecor, Director of the Statistical Laboratory of Iowa State College, Ames. Third edition. Fabrikoid. Price, \$3.75. Pp. 422, with illustrations. Ames: Iowa State College Press, 1940.

This edition appears only two years after the second. Some material has been added to the chapters on linear regression and large samples of enumeration data, while an additional chapter has been written to incorporate methods useful in some of the broader fields of sampling. Physicians without a considerable knowledge of higher mathematics will not find this book easy, but those who are advanced in the study of statistical methods may obtain much valuable information.

**The Psychological Aspects of Pediatric Practice.** By Benjamin Spock, M.D., and Mabel Huschka, M.D. [Reproduced from the Practitioners Library of Medicine and Surgery, Vol. XIII, pp. 757-808, by the New York State Committee on Mental Hygiene, Courtesy of the D. Appleton-Century Company.] Paper. Price, 25 cents. New York.

This reprint is an interesting summary useful perhaps for the pediatrician, which explains the attitudes and interests of children, particularly babies, toward feeding problems, weaning, thumb sucking, nail biting, constipation, enuresis, anxiety, temper tantrums, discipline, training and spoiling, masturbation, fears, phobias and night terrors and similar subjects. The matters are dealt with briefly from sound common sense to the scientific point of view.

**Child Care and Training.** By Marlon L. Faegre, Assistant Professor of Parent Education, and John E. Anderson, Director, Institute of Child Welfare, University of Minnesota. Fifth edition revised. Cloth. Price, \$2.50. Pp. 320, with 23 illustrations. Minneapolis: University of Minnesota Press, 1940.

This edition has been completely checked and brought down to date. The fundamental plan and information of earlier editions has been maintained. Every phase of the child's life from a year through high school is discussed clearly and concisely. Ample illustrations, references and suggestions accompany each topic. The chapters on habits, on imagination, truth and falsehood and on books and reading are especially interesting. Parents, teachers, students, doctors and others working with or interested in children have for many years valued and will continue to value this book and find it interesting, highly informative reading.

## Queries and Minor Notes

THE ANSWERS HERE PUBLISHED HAVE BEEN PREPARED BY COMPETENT AUTHORITIES. THEY DO NOT, HOWEVER, REPRESENT THE OPINIONS OF ANY OFFICIAL BODIES UNLESS SPECIFICALLY STATED IN THE REPLY. ANONYMOUS COMMUNICATIONS AND QUERIES ON POSTAL CARDS WILL NOT BE NOTICED. EVERY LETTER MUST CONTAIN THE WRITER'S NAME AND ADDRESS, BUT THESE WILL BE OMITTED ON REQUEST.

### TREATMENT OF EPIDEMIC INFLUENZA

To the Editor:—I should like your advice on the best known modern treatment for influenza.

William B. Brown, M.D., Columbia, Mo.

ANSWER.—There is no specific treatment for true epidemic influenza. Modern therapy is of necessity still symptomatic. It places a special emphasis on two points: rest in bed and good nursing care. The patient should be put to bed as early as possible after onset of the disease and kept there until convalescence is well established. The object of good nursing is to promote the comfort of the patient and to preserve his strength. The diet during the acute stage should be liquid, given at frequent intervals and not to exceed 3,000 cc. A small enema on the second or third day is preferred to purgation by cathartics. Headache and body pains are combated by judicious and restricted use of analgesics and sedatives, among which salicylates and codeine are probably most useful. The irritating cough is treated by keeping the air of the sick room moist, by inhalation of compound tincture of benzoin in steam and by expectorant and sedative drugs.

It has been established that *Haemophilus influenzae* (Pfeiffer's bacillus) is not the cause of the disease but that a virus and probably at least two strains cause epidemic influenza.

### GROWTH OF TISSUES AFTER DEATH

To the Editor:—Dr. James Ewing (in *Legal Medicine and Toxicology*, Ed. 2, Vol. 1, edited by Peterson, Haines and Webster, Philadelphia, W. B. Saunders Company, 1923, p. 175) states that the hair and finger nails may continue to grow after death. The same statement is repeated by Webster (in *Legal Med. and Toxicology*, Philadelphia, W. B. Saunders Company, 1930, chapter 4, p. 71). On the other hand, in *Legal Medicine and Toxicology* by Gonzales, Vance and Helpen (New York, D. Appleton Company, 1937, chapter 5, p. 64) the statement is made that such "growth does not continue after death as claimed by popular superstition." With such authorities at variance I would deeply appreciate the opinion of a referee.

M.D., California.

ANSWER.—Somatic death, or death of the body as an organism, occurs with cessation of the functions of the vital centers—the heart, lungs and brain. Molecular death, or death of the tissue cells, which goes on constantly during life incidental to the breaking down and building up of tissues, may not become complete at the time of somatic death but may be delayed until later. It is reasonable to believe that molecular life may continue after somatic death but for only a comparatively short time, because the oxygen cycle has been stopped. In fact, tissues such as skin and bone from the bodies of persons recently dead have been transplanted successfully to living persons. In the opinion of Sydney Smith (*Forensic Medicine*, ed. 4, London, J. & A. Churchill, Ltd., 1934, chapter 2, pp. 16-17) the period between somatic death and complete molecular death of the body tissues, while of considerable duration in such animals as frogs and eels, is in man rarely more than three or four hours.

According to popular superstition the hair and nails continue to grow after death. These tissues are highly resistant to decomposition, but medicolegal authors are divided as to whether or not growth of such structures actually occurs after somatic death. According to James Ewing (in *Legal Medicine and Toxicology* by Many Specialists, ed. 2, edited by Peterson, Haines and Webster, Philadelphia, W. B. Saunders Company, 1923, vol. 1, p. 175) and Ralph W. Webster (*Legal Medicine and Toxicology*, Philadelphia, W. B. Saunders Company, 1930, chapter 4, p. 71) growth of hair and nails continues for some time after somatic death. Irving C. Rosse (in *Medical Jurisprudence, Forensic Medicine and Toxicology*, edited by Witthaus and Becker, New York, William Wood & Co., 1894, vol. 1, pp. 406-407) also states that it is believed that hair and nails grow after somatic death. He refers to a case reported by Dr. Caldwell of Iowa in the *New York Medical Record* (Aug. 18, 1877). Dr. Caldwell claimed that he was present in 1862 at the exhumation of a body which had been buried for four years; that hair protruded through openings in the coffin where the joints had separated and that although the deceased had reputedly been shaved before burial the hair of

the head measured 18 inches, the beard 8 inches and the hair of the breast from 4 to 6 inches. Rosse also refers to a case in Washington, D. C., in which the body of a young girl, supposed to have been 12 or 13 years of age at the time of her death, was exhumed and "a number of persons noticed . . . that her hair had grown until it extended from her crown to her feet." But, according to the weight of authority and what appears to be the correct view, growth of hair and nails in a dead human body does not occur to any measurable degree after somatic death (Gonzales, Thomas A.; Vance, Morgan, and Helpen, Milton: *Legal Medicine and Toxicology*, New York, D. Appleton-Century Company, 1937, chapter 5, p. 64. Taylor's *Principles and Practice of Medical Jurisprudence*, ed. 9, edited by Sydney Smith, with revision of legal aspect by W. G. H. Cook, London, J. & A. Churchill, Ltd., 1934, vol. 1, pp. 144-145. Draper, Frank Winthrop: *A Text-Book of Legal Medicine*, Philadelphia, W. B. Saunders Company, 1905, chapter 5, p. 88). The shrinking of the skin and soft tissues after somatic death may, however, lead to extrusion of hair above the surface of the skin and thus simulate growth after death. Hence from twenty-four to forty-eight hours after death the hair on the face of a cadaver may project more above the surface of the skin than it did at the time of death. Likewise the shrinking of the skin and soft tissues after death may also cause the nails to appear longer.

### DARK ADAPTATION AND NIGHT VISION OF AVIATORS

To the Editor:—I am greatly interested in what may come out of the vague reports we begin to hear in the United States of the trial of British airmen who can see better in the dark than normal persons (hemeralopia) in the desperate night defense of London. From the time of Hippocrates and Galen, there have been among soldiers and sailors cases of so-called hemeralopia or seeing better in the dark. Always, however, there has been some ambiguity as to both proper title and etiology. Aristotle seems to have had an appreciation of its nature when he applied the name of "night fox" to those who, like foxes and other beasts or birds of prey, could see better in the dark. Now it remains, apparently, as one of England's dire necessities to try out airmen possessed of this odd quality of the sense of sight. Perhaps no tale of Jules Verne, the Arabian Nights or Swift could surpass in imagination the flight of a possible modern "night hawk" darting from cloud to cloud yet picking out his enemy's plane in the blackness of the night. How much of this are we to believe? Certain it is that a few returning travelers from England who have talked with some of the high command in British aviation speak of the actual trial of gunmen and even pilots who possess this peculiar but rare quality of seeing much better in the night than do normal persons. That a small number of such men can be found among many thousands of soldiers is unquestionably true. It remains, however, another matter entirely to put such a peculiar perception to practical use in meeting a German night air blitzkrieg. The ability to see larger objects better in darkness or dusk, rather than in a bright light, called hemeralopia, is apparently a form of so-called day blindness and needs to be studied from many angles. It occurs not only in certain chronic conditions of the retina and optic nerve but also in persons long excluded from the light and in some with congenital anomalies. Just why a few persons should be born with this tendency is not fully understood, nor can the cases as yet be readily classified. In my eye examinations of many recruits of the first World War coming before me as a member of the Dubuque Draft Board of 1917-1918, I recall but 1 definite case; the particular man could not be accepted for army duty at all because of other defects. On another occasion I took considerable time in studying the same condition in a chauffeur in Chicago. This man had served in the South African Boer war and was well known in the regiment for his rare ability to see far in the dark. For the exercise of this function he had often been stationed at important outposts of the camp during the night. The condition of the fundus of the eye at the time was diagnosed as retinitis striata. Similar reports reach physicians of certain fishermen or hunters who in this respect are the envy of their companions. So-called day blindness or hemeralopia is to be differentiated from the opposite condition, called nyctalopia or night blindness, and seems to be much more common in men than in women. Whether an advantage can be expected from men who can see an enemy's plane in the dark rather than from an air instrument that locates it more blindly may prove of more than academic value by the time Europe's second World War is over.

Henry G. Langworthy, M.D., Dubuque, Iowa.

ANSWER.—Ability to see in reduced illumination depends partly on the function of dark adaptation, by which the chemical substance which is necessary for function of the retinal rods is regenerated. A number of persons have this function reduced below normal from various causes, among which are vitamin A deficiency and pigmentary degeneration of the retina, in which the rods themselves are deficient. This constitutes the condition nyctalopia, which term is, as stated, commonly confused with the term hemeralopia. Hemeralopia, from its derivation, really means dim or confused vision in daylight. This is how the term is understood by ophthalmologists, who recognize that certain persons with defective central vision due to lesions of the central part of the retina or papillomacular bundle of the optic nerve are unable to see as well as others in the daylight, while at night, when only the peripheral portion of the retina is called on to function, they see as well as



other persons. Such persons who see poorly in daylight because of central visual defects really see no better in the dark than normal persons but may believe they do and may be actually less inconvenienced in the dark than normal persons who are customarily dependent on their good central vision.

The function of dark adaptation varies considerably in so-called normal persons. Whether this variation ever amounts to a really abnormal ability to see in the dark seems never to have been satisfactorily determined. No careful investigations of this function in persons who are reputed to have abnormally acute twilight vision, such as the aviators described, has been discovered. The most likely explanation in most cases would seem to be on the basis of such careful training to detect and interpret properly visual impressions as is seen in hunters and native guides who, with only normal lenses, are able to detect the presence of animals under conditions in which the untrained observer might see the signs but would not notice them.

Because of the confusion in terms it is probably better to refer to day blindness and night blindness rather than nyctalopia or hemeralopia.

### TREATMENT OF NASAL OBSTRUCTION

*To the Editor:*—Please advise me as to the present status of the intranasal application of estrogenic substances as used in the treatment of local nasal disturbances. A western rhinologist told me last winter that he had considerable success in combating symptoms of nasal edema and swelling with this material when the condition could not be traced to allergy. I have in mind a woman of 19 who had a thyroidectomy seven years ago on account of toxic adenoma with recurrence and reoperation six months ago. Beginning some time before the last operation she has complained of frequent "stoppage" of the nostrils during both day and night. This has not been affected by several vacations into other and distant localities, and usual methods have so far failed to give evidence that the condition is allergic in nature. Some time ago she consulted a rhinologist, who performed a submucous resection of the septum. Since that time she has been suffering more than before. Except as noted, there is no evidence of any physical impairment. M.D., North Carolina.

**ANSWER.**—From the description given, the chief complaint seems to be nasal obstruction not due to allergy nor caused by an obvious suppurative in the accessory nasal sinuses. The most likely venture as to the cause of the trouble would be that it is a tumescent rhinitis.

The diagnosis can easily be confirmed by examining the nose before and after the use of some adequate astringent. If there is a definite change after the use of such an astringent, and the mucosa is thoroughly shrunken, rational treatment would be cauterization of one type or another. Should astringents fail to shrink the mucosa of the nose, a diagnosis of chronic hypertrophic rhinitis would be reasonable. Such a condition is either localized, as would be evidenced by seeing hypertrophied posterior ends, or it would be seen throughout the length of the inferior turbinate.

Estrogenic substances used locally have not been recommended for these conditions. They have found their chief use in atrophic rhinitis, in which, in a number of instances, after a fair trial the mucosa has resumed its normal turgidity.

### EXFOLIATIVE DERMATITIS

*To the Editor:*—A man aged 57 visited a dermatology clinic for what appeared to be a seborrheic dermatitis of the face and scalp. His head and face were treated with roentgen rays and he was given an ointment of sulfur and salicylic acid to apply on the affected area and a resorcinol shampoo for the scalp. The face was burned by the roentgen treatment and the skin began to desquamate. In about a week the lesion had spread to the chest and groin and in another week covered the entire body. There was intense itching and burning and of course abundant exfoliation, so that the diagnosis was plainly an exfoliative dermatitis. The condition has existed for two months and the patient suffers considerably from itching and burning. Treatment has been directed toward relief of these symptoms with colloidal baths and bland oils. The etiology is entirely obscure, as he had been taking no medicine and enjoyed good health prior to this affliction. Would you discuss treatment and prognosis of this disease?

John W. O'Neill, M.D., St. Charles, Mich.

**ANSWER.**—Exfoliative dermatitis may result from the taking of drugs by mouth or parenterally, e. g. arsenic or its compounds, or may occur as a consecutive phenomenon following local applications of an irritant nature to a preexisting dermatitis, e. g. psoriasis, lichen planus, dermatitis venenata or eczema. It may also be the precursor of one of the entities in the lymphoblastoma group (since the condition described has existed for two months); the type resulting from irritation due to external applications usually disappears in the course of a few weeks. The local treatment consists in the use of soothing applications and cessation of all local irritants or drugs that may be a contributory factor. Colloid, alkaline or bran baths are of value, together with the free anointment of the body with bland sooth-

ing salves, e. g. borated cold cream, or the general use of Pusey's calamine liniment or a simple lime water-olive oil emulsion. Intravenous injections of 10 per cent sodium thiosulfate solution is also a valuable adjunct to soothing local therapy. The general health of the patient should receive attention and the history should be carefully checked regarding the previous accidental ingestion of arsenic. If, in spite of conservative treatment, the exfoliative dermatitis persists, one must rule out the possibility of an eruption in the lymphoblastoma group, and blood examinations and microscopic examination of a gland should be done together with microscopic examination of the skin. The prognosis in the latter group of conditions is only fair.

### RESULTS OF ELECTRIC SHOCK FROM X-RAY APPARATUS

*To the Editor:*—About eight days ago while assisting our roentgen ray technician with a patient I received a severe electric shock which knocked me unconscious to the floor. I was wearing my head mirror at the time and was standing near the patient. It is possible that my head mirror touched the wiring (we have an old Kelly-Koett which is not shockproof), since the current burned a deep hole in my head just over my right eye and singed the rest of my forehead. I regained consciousness within a few seconds but remained dazed for about two hours. Since this accident I have suffered with a headache which encircles my whole head but is more severe over my right eye. Medications do not relieve it. I have continued to work (eye, ear, nose and throat) but the headache continues and I am miserable. My sinuses and eyegrounds were checked and found to be all right. I might mention that the technician received a lesser shock while the patient received none. 1. Can you tell me what is causing the headache? Is it edema? 2. How long will it continue and what should be taken if anything for relief? 3. Are there chances of cataracts developing? If so, when do they appear? 4. Will there be any permanent damage to the brain manifesting itself later? I would appreciate any help that you can give and any references that you may wish me to consult on the subject. We were using a 30 milliamper tube and taking a picture of the lower jaw for a possible calculus in the submaxillary duct.

Michael T. Palen, M.D., Roanoke, Va.

**ANSWER.**—1. Edema of the brain is an infrequent complication. The usual results of severe electric shocks involving the head result in loosening of the glia and vacuolation of the nerve cells with a slight destruction of the Nissl bodies. The media of the capillaries and the blood vessels might be slightly involved. These are probably the results of increased temperature incidental to an electric shock. These end results might be the cause of the headache and, as an additional cause, the destruction of the soft tissues above the eye may be partly responsible with transmission of sensations to the peripheral nerves. These changes are not dangerous and will subside on healing of the external wound and the recuperation of the neuroglia and vacuolation of the cells, the latter taking an approximate period of three weeks to several months.

2. This question is partly answered under 1. No additional therapeutic measures are necessary, excepting the customary treatment of any superficial wound.

3. The development of cataracts is a rare incident. If it is going to occur it usually happens within the first three weeks.

4. This was partly answered under 1. However, in amplification, it can be anticipated that no permanent damage to the brain will occur.

An interesting article written by R. H. Jaffe, M.D., entitled "Electropathology," was printed in the *Archives of Pathology* (5:837 [May] 1928).

### PROSTATIC HYPERPLASIA AND URETHRAL DILATORS

*To the Editor:*—Please give me an opinion on the "oscillatherm" for prostate work. This is manufactured by the Oscillatherm Company, 333 West Second Street, Los Angeles. What do you think of prostate therapy by this means and also what are the best appliances used? Please give me a list of good urethral dilating instruments. What is thought about the compound dilator, i. e. the type that has an adjustable screw to cause the formation of any size dilator? In my practice I have occasion to use dilating instruments to overcome strictures. I also have a good many patients with benign prostatic hypertrophy and would like to know if an instrument of the oscillatherm type has any merit.

A. E. Sprafka, M.D., Detroit Lakes, Minn.

**ANSWER.**—There are many instruments on the market which are supposed to apply heat to the prostate gland and which are of doubtful therapeutic value. The best method of applying heat is by means of diathermy. Neither diathermy nor any other method of applying heat to the prostate gland is of much value in the treatment of prostatic hyperplasia and urinary obstruction. It may, however, be of some value in the treatment of prostatitis when used with prostatic massage. In some cases prostatic hyperplasia can be reduced by the use of androgen, but the degree of urinary obstruction is seldom completely or permanently diminished. Prostatic obstruction which causes



# The Journal of the American Medical Association

Published Under the Auspices of the Board of Trustees

VOL. 116, No. 4

COPYRIGHT, 1941, BY AMERICAN MEDICAL ASSOCIATION  
CHICAGO, ILLINOIS

JANUARY 25, 1941

## SULFATHIAZOLE AND SULFAPYRIDINE

IN THE TREATMENT OF PNEUMONIA IN INFANCY  
AND CHILDHOOD

STEWART C. WAGONER, M.D.

AND

WILLIAM F. HUNTING, M.D.

CINCINNATI

Sulfathiazole [2 (para-amino-benzene-sulfonamido)thiazole], the thiazole derivative of sulfanilamide, has been offered to the medical profession for clinical trial. Experimental work, both in vitro and in vivo, by Barlow and Homburger,<sup>1</sup> McKee, Rake, Greep and van Dyke,<sup>2</sup> Long and Bliss,<sup>3</sup> and others has indicated that it probably is as effective in the treatment of pneumonia and certain other infections as sulfapyridine. Studies on the toxicity of the drug in animals by Long, Haviland and Edwards<sup>4</sup> and van Dyke, Greep, Rake and McKee<sup>5</sup> indicated that the drug could probably be safely used clinically under carefully controlled conditions. During the past two years numerous articles have appeared which would seem to indicate that sulfapyridine is an effective agent in the treatment of pneumonia. Among these publications was that of Wilson, Spreen, Cooper, Stevenson, Cullen and Mitchell<sup>6</sup> at the Children's Hospital and in the pediatric wards of the Cincinnati General Hospital, in which there was a study of a group of patients receiving sulfapyridine and a control group not receiving this drug. The present report is a study of the relative effectiveness of sulfapyridine and sulfathiazole in the treatment of pneumonia in infancy and childhood.

The patients were allocated to one of two groups on admission, designated respectively as "sulfapyridine" and "sulfathiazole," in such a manner that after completion of the study the two groups would be comparable, at the time therapy was instituted, in regard to age and duration and severity of the pneumonia. No attempts were made to differentiate between croupous pneumonia and bronchopneumonia. Because of possible differences of assimilation of sulfapyridine and sulfathia-

zole, it was decided to make the comparison between their effects on the basis of the levels of the free drug in the blood. From the work done last year by Wilson and his co-workers it was felt that a level of free sulfapyridine in the blood of from 4 to 6 mg. per hundred cubic centimeters was therapeutically adequate, and it was accordingly decided to attempt to administer sulfapyridine and sulfathiazole in this study in doses which would keep the blood concentration between these levels. The majority of patients were started on 1 grain (0.06 Gm.) of sulfapyridine per pound (0.5 Kg.) of body weight and 1½ to 2 grains (0.1 to 0.13 Gm.) of sulfathiazole per pound (0.5 Kg.) of body weight. Daily blood levels were ascertained, and the dose was altered accordingly so that the blood levels would be properly maintained.

On admission the material for pharyngeal cultures for pneumococci, cultures of the blood, roentgenograms of the chest and complete blood cell counts were obtained on all patients, and other studies and cultures were done as indicated. Chemotherapy was instituted immediately, half the calculated dose for twenty-four hours being given as an initial amount, and thereafter the drug was administered every four hours as long as indicated, except in a few instances when it was given every three hours or every eight hours.

All patients were studied closely in both groups, my colleague and I keeping in mind the final analyses to be made and the observations to be recorded. Those patients who had empyema on admission were excluded from the series, but those who had sterile pleural effusions were included in the final group. Four patients were discarded from the final analysis since in their cases the diagnoses were subsequently proved to be tuberculous pneumonia. None of these patients showed any response to chemotherapy. It was decided not to evaluate the day of clinical improvement since it was much less of an objective determination than the day of significant fall in temperature, although both fall in temperature and apparent clinical improvement occurred on the same day except in a few instances.

Most clinicians have agreed that a fall in temperature should occur within forty-eight hours if it is to be attributed to chemotherapy. In this study all patients whose temperatures were not below 100 F. (37.5 C.) in forty-eight hours and then remained below this level were designated as having an unsatisfactory response. All patients received the drug continuously until the temperature had remained below 100 F. rectally for seventy-two hours.

During the course of the study, daily physical examinations were made and special graphic records were kept of all physical and noteworthy changes. Daily estimations were made of the blood level of the drug on 0.2 cc. of capillary blood by using a photoelectric colorimeter and a modification of the method of Marshall

E. R. Squibb & Sons furnished the sulfathiazole used in this study.  
From the Children's Hospital Research Foundation and the Department of Pediatrics, University of Cincinnati College of Medicine.  
Advice regarding the statistical methods employed was given by Estelle W. Brown, statistician of the Children's Hospital Research Foundation.

1. Barlow, O. W., and Homburger, E.: *Proc. Soc. Exper. Biol. & Med.* 42: 792 (Dec.) 1939.

2. McKee, Clara M.; Rake, Geoffrey; Greep, R. O., and van Dyke, H. B.: *Proc. Soc. Exper. Biol. & Med.* 42: 417 (Nov.) 1939.

3. Long, P. H., and Bliss, Eleanor A.: *Proc. Soc. Exper. Biol. & Med.* 43: 324 (Feb.) 1940.

4. Long, P. H.; Haviland, J. W., and Edwards, L. B.: *Proc. Soc. Exper. Biol. & Med.* 43: 328 (Feb.) 1940.

5. van Dyke, H. B.; Greep, R. O.; Rake, Geoffrey, and McKee, Clara M.: *Proc. Soc. Exper. Biol. & Med.* 42: 410 (Nov.) 1939.

6. Wilson, A. T.; Spreen, A. H.; Cooper, M. L.; Stevenson, F. E.; Cullen, G. E., and Mitchell, A. G.: Sulfapyridine in Treatment of Pneumonia in Infancy and Childhood, *J. A. M. A.* 112: 1435 (April 15) 1939.

and Litchfield.<sup>7</sup> Following the blood count on admission, hemoglobin determinations and leukocyte counts were made every three days unless they were indicated more frequently, and daily urinalyses were done in most cases.

#### ANALYSIS OF MATERIAL

One hundred and nine patients with pneumonia were treated and the results analyzed in the manner outlined.

TABLE 1.—Analysis of 109 Cases of Pneumonia

	Sulfathiazole Group (Total 55)	Sulfapyridine Group (Total 54)
Age		
Birth to 11 months.....	7	4
12 to 23 months.....	18	17
2 to 4 years.....	14	19
5 years and over.....	16	14
Severity		
Mild.....	3	5
Moderate.....	30	32
Severe.....	21	16
Very severe.....	1	1
Estimated duration of pneumonia when therapy was started		
1 day.....	4	6
2 days.....	22	21
3 days.....	17	17
4 days.....	10	7
5 days.....	1	2
6 days.....	1	1
Average.....	2.7	2.6
Type of pneumonia		
Croupous.....	13	12
Bronchopneumonia.....	42	42

Of these patients 55 received sulfathiazole and 54 received sulfapyridine. Table 1 demonstrates the comparison between the two groups, related to age and to the severity and duration of pneumonia, when the treatments were started. While no attempt was made to differentiate between croupous pneumonia and bronchopneumonia in grouping the cases, table 1 also shows how closely these two types were distributed by chance alone.

As previously stated, the "sulfapyridine group" was started on 1 grain per pound of body weight per twenty-four hours, the initial dose being one half of the calculated twenty-four hour dose. The "sulfathiazole group" received from 1½ to 2 grains per pound of body weight per twenty-four hours and, similarly, one half of the

TABLE 2.—Analysis of Determinations of Drugs in the Blood

	Mean	Standard Deviation
Free, mg. per 100 cubic centimeters		
Sulfathiazole.....	5.3	1.8
Sulfapyridine.....	6.3	2.5
Conjugate, mg. per 100 cubic centimeters		
Sulfathiazole.....	1.1	0.46
Sulfapyridine.....	1.6	1.00
Total, mg. per 100 cubic centimeters		
Sulfathiazole.....	6.4	2.0
Sulfapyridine.....	7.9	2.7
	Average Number of Days of Therapy	
Sulfathiazole.....	4.7 days	
Sulfapyridine.....	4.6 days	

calculated twenty-four hour dose initially. Considerable difficulty was encountered in attempting to regulate the level of the free drug in the blood to between 4 and 6 mg. per hundred cubic centimeters, and it was often necessary to change the dose daily. Table 2 shows that the average number of days of treatment in both groups was essentially the same, namely, four and seven-tenths days with sulfathiazole and four and six-tenths days with sulfapyridine.

The daily blood levels of the drugs were analyzed in both series, and the results are given in table 2. The mean level of free sulfapyridine was slightly higher, i. e. 6.3 mg. per hundred cubic centimeters, but showed a standard deviation of 2.5 as compared with sulfathiazole, of which a mean level of 5.3 mg. per hundred cubic centimeters was found, and the standard deviation was 1.8. If they are analyzed statistically there is a significant difference between the two free levels, and the probability (P) is 0.02 that this difference is due to chance alone.

Table 3 shows the organisms observed in the cultures of material from the pharynx. No intensive bacteriologic study was made in this series other than the routine cultures on admission, and the number of pathogenic organisms found is less than that reported by other workers by whom more emphasis was placed on this factor. The number of cases is too few to warrant an analysis of the type of organism in relation to severity type of pneumonia or effect of therapy.

Of the 109 patients only 2 were found to have bacteremia on admission, both being in the sulfathiazole

TABLE 3.—Types of Organisms Isolated from Throats\*

Type of Organism	Sulfathiazole Group	Sulfapyridine Group
Pneumococcus type:		
I.....	3	4
II.....	2	0
III.....	0	1
IV.....	0	3
V.....	4	0
VI.....	6	3
VII.....	1	0
IX.....	1	1
XI.....	1	2
XIV.....	1	3
XV.....	1	1
XVI.....	1	1
XVII.....	1	0
XVIII.....	2	3
XIX.....	4	4
XXIII.....	0	1
XXV.....	1	0
XXVIII.....	1	0
XXX.....	1	0
XXXIII.....	1	0
Hemolytic streptococcus.....	5	4
Hemolytic Staphylococcus aureus.....	6	4
Nonpathogenic or negative culture.....	16	27

\* This includes all pneumococci observed, whether alone or in combination with other types.

group and in the younger age group. The causative organisms in these patients were type II and type XXXIII pneumococci respectively. Both patients subsequently recovered.

There were two deaths during the course of this study. One death was of an infant aged 15 months who was moribund on admission and who had bilateral bronchopneumonia and active rickets. The throat culture yielded type XXXIII pneumococcus. The serum calcium level was 3.8 mg. per hundred cubic centimeters, and the phosphorus level was 9.1 mg. on admission, although there was no clinical evidence of tetany. The patient received two doses of sulfathiazole but died thirteen hours later. Permission for necropsy was refused. This patient was excluded from the final analysis of the series. The other patient was an infant aged 13 months with extensive bilateral bronchopneumonia. The throat culture yielded type I pneumococcus. There was an initial response to the drug with a fall in temperature, but the infant died suddenly twenty-seven hours after admission. At necropsy an extensive bilateral bronchopneumonia and a dilated right ventricle and auricle were the only positive manifestations. This patient was included in the study.

7. Marshall, E. K., Jr., and Litchfield, J. T., Jr.: Science 88:85 (July 22) 1938.

# ANALYSIS OF THE RESULTS

1. *Course of the Pneumonia.*—Table 4 demonstrates the average day for both sulfathiazole and sulfapyridine groups on which there was a significant fall in temperature and also the day of clinical recovery in relation to the day of the onset of pneumonia and the day of beginning of treatment. The two drugs appeared to be equally effective, and the difference in days between the two groups is not statistically significant in any of the analyses. In both groups, the significant fall in temperature was approximately thirty-six hours after treatment was started, and clinical recovery occurred on the average of five and one-half days following the beginning of drug administration in the sulfathiazole group and six and two-tenths days in the sulfapyridine group. The temperature of 55 patients treated with sulfathiazole fell within twenty-four hours to below 100 F. (37.5 C.) rectally and remained below this level in 44 cases, whereas, excluding the 1 patient who died, this fall in temperature occurred within twenty-four hours in only 32 of the 53 patients in the sulfapyridine group. This difference between the two groups is not statistically significant and in a series of this size could well be due to chance alone. It may be mentioned, however, that clinical observation suggested that there was a better response to sulfathiazole than to sulfapyridine.

TABLE 4.—Clinical Results in 109 Cases of Pneumonia

	Sulfathiazole Group	Sulfapyridine Group	Difference in Days
Mean day of pneumonia at Significant fall in temperature	3.90	4.30	0.40
Clinical recovery	9.2	8.9	0.3
Mean day of treatment at Significant fall in temperature	1.5	1.4	0.1
Clinical recovery	5.5	6.2	0.7

2. *Drug Response Unsatisfactory: Failures and Relapses.*—Of the group of 55 patients treated with sulfathiazole 2 apparently showed an unsatisfactory response to this therapy, since their temperatures failed to fall below 100 F. (37.5 C.) rectally within forty-eight hours. Of the 53 patients in the sulfapyridine group there were 8 who failed to show the drop in temperature within forty-eight hours. This apparent difference in favor of sulfathiazole was analyzed statistically and chi square was found to be 2.96 and P to be between 0.10 and 0.05. Therefore it must be stated that in a series of this size there probably is no significant difference between the number of unsatisfactory responses in the two groups. One of the patients in the sulfathiazole group and 2 in the sulfapyridine group had relapses. All 3 of these patients had shown an initial satisfactory response but manifested a rise in temperature and a return of symptoms when chemotherapy was discontinued. One patient in the sulfathiazole group failed to respond and, although receiving the drug continuously, did not become afebrile until after fifteen days of such treatment.

Three patients who were originally included in the study were excluded in the final analysis. Two of these patients received sulfapyridine for three days but manifested a progression of symptoms. A change was made to sulfathiazole therapy and the temperature promptly fell to normal within twenty-four hours and marked clinical improvement was evident. Cultures taken on material from the throat yielded hemolytic *Staphylococcus aureus* and pneumococcus type XVII. The other patient received sulfathiazole for three and one-half days

with no effect. Sulfapyridine therapy was then started and the temperature fell to normal in thirty-six hours with resultant clinical improvement. Type IV pneumococcus was found on cultures of material taken from the throat. These significant falls in temperature may have been only coincidental crises in the normal course of pneumonia but they suggest the advisability of changing

TABLE 5.—Complications in 109 Cases of Pneumonia

	Sulfathiazole Group		Sulfapyridine Group	
	On Admission	After Admission	On Admission	After Admission
Empyema	0	0	0	1
.....	2	0	0	0
.....	6	0	4	3
.....	8	1	6	5
.....	1	0	2	0
.....	0	..	1	..
.....	2	0	1	0

ing drugs when the response is unsatisfactory to one or the other of them.

## INCIDENCE OF COMPLICATIONS

Table 5 is an analysis of complications in the two groups of patients. The series is too small to permit one to evaluate any difference in these findings, although there is an apparent difference between the two groups in the incidence of nonsuppurative otitis media which occurred after admission. Of the 55 patients in the sulfathiazole group there was 1 who had acute nonsuppurative otitis media, and in the 54 patients in the sulfapyridine group there were 5 who had this complication. Empyema developed in one patient in the sulfapyridine group.

## TOXIC EFFECTS OF SULFAPYRIDINE AND SULFATHIAZOLE

In 1 patient cyanosis developed after the administration of sulfathiazole, but after the administration of sulfapyridine it developed in 3 patients. None of these patients manifested cyanosis on admission and it occurred subsequent to initial clinical improvement, thus suggesting that it was due to the drug.

Ten patients in the sulfathiazole group and 5 patients in the sulfapyridine group had cyanosis on admission

TABLE 6.—Toxicity of Drug as Shown by Incidence of Vomiting

Number of patients who vomited							
Sulfathiazole group	.....	.....	.....	.....	.....	.....	18
Sulfapyridine group	.....	.....	.....	.....	.....	.....	34
Number of times	1	2	3	4	5	6	7
Sulfathiazole group	10	3	3	1	1		
Sulfapyridine group	9	13	5	2	3	1	1
Median for sulfathiazole group	.....	.....	.....	.....	.....	.....	1.9
Median for sulfapyridine group	.....	.....	.....	.....	.....	.....	2.5

which disappeared with clinical improvement and a significant fall in temperature, thus suggesting that it was due to the pneumonia.

Microscopic hematuria appeared in only 1 patient in the sulfathiazole group and in no patient in the sulfapyridine group.

No instances of hemolytic anemia were discovered. Leukopenia was noted in 2 patients, 1 in each group. A leukocyte count of 4,900 was found in 1 patient on the fifth day of treatment with sulfathiazole and a leukocyte count of 3,600 in 1 patient on the third day of treatment

with sulfapyridine. Therapy was discontinued immediately when the leukopenia was discovered, and the leukocyte count promptly returned to normal levels.

No morbilliform rash or other type of rash occurred which could be attributed to drug therapy.

Vomiting was the chief toxic manifestation noted. It was observed in 18 patients treated with sulfathiazole and in 34 treated with sulfapyridine. Table 6 indicates the incidence of this symptom and shows that in those who vomited it occurred on the average one and nine-tenths times in the sulfathiazole group and two and five-tenths times in the sulfapyridine group. How much of the vomiting was due to the pneumonia and how much due to the administration of the drug cannot be determined.

#### SUMMARY AND CONCLUSIONS

1. A control study of pneumonia in infancy and childhood was made on two comparable groups, one receiving sulfathiazole and the other sulfapyridine. No control group of nonspecifically treated patients was included since the efficacy of chemotherapy in pneumonia in general is well established. Careful selection was made to assure comparable groups in relation to the factors of age and duration and severity of pneumonia and the time at which the drug therapy was started. For comparison an attempt was made to adjust the levels of the free drug in both groups to between 4 and 6 mg. per hundred cubic centimeters.

2. One hundred and nine patients with pneumonia were observed in this study, 55 of whom received sulfathiazole and 54 sulfapyridine. An analysis of the characteristics of the disease on admission and of the levels of the free drug in the blood achieved demonstrated that the two groups were suitable for comparison.

3. No significant statistical difference was demonstrated between sulfathiazole and sulfapyridine in relation to the time at which a significant fall of temperature occurred or the time at which there was clinical recovery. In the sulfathiazole group the mean time after treatment at which the temperature fell to below 100 F. (37.5 C.) and remained below this level was one and five-tenths days; in the sulfapyridine group it was one and four-tenths. In the sulfathiazole group the mean time at which there was apparent clinical recovery was five and five-tenths days; in the sulfapyridine group it was six and two-tenths.

4. Unsatisfactory response to the drug occurred in 2 patients in the sulfathiazole group and in 8 patients in the sulfapyridine group. This is probably not a statistically significant difference. There was one relapse in the sulfathiazole group and there were two relapses in the sulfapyridine group. One patient treated with sulfathiazole followed a course apparently uninfluenced by the drug.

5. It is suggested that a change might be made from one drug to the other in those instances in which a significant fall in temperature fails to occur within forty-eight hours after therapy is started, or that serum therapy might then be employed.

6. There was one death of a patient treated with sulfapyridine. Empyema subsequently developed in another patient after an initial good response to sulfapyridine.

7. Vomiting occurred in 18 patients treated with sulfathiazole and in 34 patients treated with sulfapyridine, but an evaluation of the incidence of this symptom as a toxic effect of the drugs is confused by the fact that pneumonia itself is a cause of vomiting. Hematuria

developed in 1 patient while taking sulfathiazole. Leukopenia occurred in 1 patient taking sulfathiazole and in 1 patient taking sulfapyridine.

8. This study indicates that sulfathiazole is as effective as sulfapyridine in the treatment of pneumonia. No marked toxicity was noted from the administration of sulfathiazole or of sulfapyridine when it was administered over an average period of five days.

Elland Avenue and Bethesda.

### SULFAPYRIDINE THERAPY IN LOBAR PNEUMONIA ASSOCIATED WITH LEUKOPENIA

CHARLES K. FRIEDBERG, M.D.

NEW YORK

When lobar pneumonia is associated with leukopenia instead of the usual leukocytosis, a therapeutic problem is presented as to the propriety of administering sulfapyridine. On the one hand it is known that sulfapyridine itself is capable of producing serious or even fatal leukopenia and neutropenia. Thus there would seem to be a justifiable hesitation in using this drug, lest it further depress the low leukocyte count to a dangerous degree. On the other hand, sulfapyridine is probably the most valuable single agent in the treatment of lobar pneumonia. Its use appears particularly indicated in cases of lobar pneumonia with leukopenia because these cases usually represent severe infections and present the worst prognosis. Middleton and Gibbon<sup>1</sup> noted that all their patients with leukopenia of less than 5,000 leukocytes per cubic millimeter died. Even those patients with relative leukopenia (5,000 to 10,000 leukocytes per cubic millimeter) had a much higher mortality rate than those with leukocytosis. The most extreme example of leukopenia associated with lobar pneumonia was a fatal case, reported by Menninger,<sup>2</sup> in which the leukocyte count was as low as 150 per cubic millimeter.

The danger of sulfapyridine leukopenia or neutropenia is relatively slight. Large series of patients with lobar pneumonia have been treated with sulfapyridine without the occurrence of this hematologic complication. There is no evidence in the reported cases that sulfapyridine leukopenia appeared more readily when the initial leukocyte count was low than when it was considerably elevated. Furthermore, in almost all cases leukopenia and neutropenia appeared only after the drug had been administered for two weeks or longer and in a total dose of 50 Gm. or more. This is a longer period of administration and a larger quantity than is ordinarily required in the treatment of lobar pneumonia. Finally it should be emphasized that leukopenia in cases of lobar pneumonia is the result of the infection itself and that any measure, such as the administration of sulfapyridine, which tends to overcome the infection should benefit the leukopenia by removing the causative factor.

In the following two cases of severe lobar pneumonia associated with striking leukopenia, sulfapyridine therapy was followed by a rise in the patient's leukocyte

From the Medical Service of Dr. George Baehr, the Mount Sinai Hospital.

1. Middleton, Richard, and Gibbon, J. H., Jr.: The Prognostic Value of the Initial Leukocyte and Differential Count in Lobar Pneumonia. *Am. J. M. Sc.* 180: 31 (July) 1930.

2. Menninger, W. C.: Extreme Leukopenia in Lobar Pneumonia. *J. A. M. A.* 85: 435 (Aug. 8) 1925.



count and clinical improvement after the usual forms of therapy, including massive doses of specific antipneumococcus serum, had been ineffective.

## REPORT OF CASES

CASE 1.—A Negro laborer aged 40 was admitted to the hospital on April 24, 1940. There was a history of persistent alcoholism and vagrancy. For two months prior to admission he had been consuming about a quart of corn whisky daily. Ten days before admission he had been suffering from an infection of the upper part of the respiratory tract.

The present illness began acutely three days before admission with severe cough, the expectoration of bloody sputum and pain in the chest. Intense headache, fever and malaise soon followed. The patient was hospitalized because of continued fever, cough and prostration.

On admission the patient appeared acutely ill. His temperature was 103.6 F., respiratory rate 44 and pulse rate 120. There was herpes of the lips. The pharyngeal mucosa was congested. There were signs of consolidation over the middle and lower lobes of the right lung. The remainder of the examination was negative. The diagnosis was lobar pneumonia of the lower and middle lobes of the right lung.

About half an hour after an initial dose (3 Gm.) of sulfathiazole had been administered a blood count revealed 1,400 white blood cells per cubic millimeter, with 7 per cent neutrophils, 14 per cent lymphocytes, 7 per cent monocytes and 1 per cent myelocytes. An hour later a count showed 1,000 white blood cells per cubic millimeter. Because of the intense leukopenia, chemotherapy was discontinued after the single initial dose of sulfathiazole. The sputum, by the direct Neufeld method, was found to contain type II pneumococci. Innumerable colonies of type II pneumococci were grown from the blood. The patient was given 400,000 units of type II antipneumococcus rabbit serum intravenously within seven hours on the evening of admission.

The next day (April 25) the patient's condition became critical. The pneumonic consolidation spread to the upper lobe of the right lung. There were symptoms and signs of pulmonary edema. The patient experienced a chill and a rise of temperature to 104 F. Because of intense dyspnea he was placed in an oxygen tent. A blood count on April 25 showed 700 white blood cells per cubic millimeter. A transfusion of blood was given. Because of the patient's critical state and his failure to respond to large doses of antipneumococcus serum after

resolution appeared throughout the right lung. A remarkable leukocytosis developed, the leukocyte count increasing on successive days to 10,000, 23,000, 28,000, 43,000 and finally to a high point of 58,000 six days after the administration of sulfapyridine was begun. Thereafter the leukocyte count fell gradually. On the thirteenth day of the illness evidences of serum sickness and nephritis appeared. These are now disappearing. At the present time the patient has a low grade fever and shows signs of delayed resolution and pleural effusion.

TABLE 2.—Blood Counts and Chemotherapy in Case 2

Date	Hemo- globin, per Cent	Leuko- cytes	Neutro- phils, per Cent	Lym- pho- cytes, per Cent	Mono- cytes, per Cent	Eosino- phils, per Cent	Sulfa- thia- zole, Gm.	Sulfa- pyri- dine, Gm.
2/25	75	10,000	84	16	..	..	6	..
2/26	67	2,900	79	14	7	..	6	..
2/27	73	6,000	70	25	5	..	..	..
2/28	76	6,800	78	9	12	1	..	..
2/29	71	10,900	70	19	9	2	..	5
3/1	81	13,700	72	20	8	..	..	6
3/2	..	7,600	84	10	4	2	..	2
3/3	..	..	..	..	..	..	..	3
3/4	58	8,500	74	16	9	1	..	7
3/5	..	..	..	..	..	..	..	5
3/6	73	11,900	64	29	7	..	..	4
3/7	..	6,600	72	20	8	..	..	1 1/2
3/10	68	13,700	..	..	..	..	..	2
3/11	72	10,600	74	20	6	..	..	6
3/12	..	..	..	..	..	..	..	4
3/13	72	7,000	47	38	12	3	..	2
3/14	..	..	..	..	..	..	..	2
3/15	..	..	..	..	..	..	..	2
3/16	..	..	..	..	..	..	..	2
3/17	..	..	..	..	..	..	..	2
3/18	75	11,100	68	32	8	2	..	..
5/3	80	7,850	64	28	11	7	..	..

CASE 2.—A Puerto Rican man aged 66 was admitted to the hospital Feb. 25, 1940. His past history was not relevant. Five days before admission he suffered generalized aches followed by a shaking chill, fever, cough and pain in the chest. He was brought to the hospital because of continued fever, anorexia, thirst, headache, intensified cough and weakness.

On admission the patient's temperature was 103.4 F., respiratory rate 26 and pulse rate 110. There were dullness, diminished breath sounds, focal areas of bronchovesicular breathing and scattered moist rales over the lower lobes of both lungs. The clinical diagnosis was bilateral lower lobe bronchopneumonia or lobar pneumonia.

The next day the patient was completely prostrated. There were frank signs of consolidation over both lower lobes. The sputum revealed type I pneumococci, and innumerable colonies of the same organism were grown from the blood. A blood count on February 25 revealed 10,000 white blood cells per cubic millimeter, of which 84 per cent were neutrophils and 16 per cent lymphocytes. Sulfathiazole therapy was begun. The next day, after 11 Gm. of sulfathiazole had been administered, the patient was found to have 2,900 white blood cells per cubic millimeter, with 79 per cent neutrophils. Because of the leukopenia, sulfathiazole was discontinued, and 400,000 units of type I rabbit antipneumococcus serum was given intravenously.

On February 29 the patient's condition appeared worse, despite specific therapy. The signs in his lungs became more extensive. Because the prognosis seemed extremely unfavorable and because the leukocyte count had risen to 10,900 per cubic millimeter, sulfapyridine therapy was begun in doses of 1 Gm. every four hours. Within twenty-four hours, the patient's temperature fell precipitously, and his clinical condition improved rapidly. After an initial rise to 13,700 the leukocyte count fell to 7,600 and then varied between 12,000 and 6,700 per cubic millimeter. The pneumonia cleared rapidly, but the patient's stay in the hospital was protracted because of pain in the lower portion of the back and spikes of fever, which were later found to be due to an inflammatory lesion of the lumbosacral region of the spine, probably a pneumococcal osteomyelitis. Before the patient left the hospital he was again given 11 Gm. of sulfathiazole in divided doses, as on admission, to determine the presence of a special sensitivity to this drug, but there was no effect on his blood count.

TABLE 1.—Blood Counts and Chemotherapy in Case 1

Date	Hemo- globin, per Cent	Leuko- cytes	Neutro- phils, per Cent	Lym- pho- cytes, per Cent	Mono- cytes, per Cent	Myelo- cytes, per Cent	Sulfa- thia- zole, Gm.	Sulfa- pyri- dine, Gm.
4/24	70	1,400 1,000	78	14	7	1	3	..
4/25	69	700	67	25	5	3	..	6
4/26	80	5,900	84	8	3	5	..	10
4/27	85	10,000	93	5	2	..	..	7
4/28	75	23,000	95	4	1	..	..	7
4/29	..	28,500	..	..	..	..	..	7
4/30	64	45,000	83	7	6	5	..	6
5/1	56	58,000	89	5	1	5	..	6
5/2	45	35,000	81	15	4	2	..	3
5/3	51	37,800	94	2	4	..	..	..
5/4	53	..	..	..	..	..	..	..
5/5	..	30,000	88	12	..	..	..	..
5/13	46	10,400	72	21	7	..	..	..

forty-eight hours of hospitalization it was decided to administer sulfapyridine, despite the severe leukopenia. Within twelve hours the patient received 10 Gm. of sodium sulfapyridine intravenously and 7 Gm. orally. Thereafter, 1 Gm. was given orally every three hours. A blood level of 11.5 mg. of sulfapyridine was attained.

Within twenty-four hours after sulfapyridine therapy was begun the patient's general condition improved strikingly. His temperature fell sharply, the maximum on the second day being 101.8 F. A blood count on April 27 showed 5,900 white blood cells, of which 84 per cent were neutrophils, 8 per cent lymphocytes, 3 per cent monocytes and 5 per cent myelocytes. From then on the patient's condition continued to improve. Signs of

## COMMENT

In both cases the patients were critically ill; they had failed to respond to specific pneumococcus antiserum, and their clinical improvement may be fairly attributed to the use of sulfapyridine. Many of the elements in both cases are those associated generally with a high mortality, viz. the multiplicity of lobes involved, the bacteremia, the extreme number of colonies in the blood cultures, the leukopenia, the poor clinical condition and, in the second case, the advanced age of the patient.

The severity of the infection supports the interpretation that the leukopenia in these cases was due to pneumonia and pneumococcic bacteremia. There was no history of the ingestion of drugs which might have caused leukopenia before admission to the hospital. In the first case the prolonged and excessive consumption of alcohol may have damaged the bone marrow and predisposed the patient to leukopenia, as suggested by Samuels and Lambert.<sup>3</sup> The single dose of sulfathiazole given to the first patient, almost simultaneously with the first examination of the blood, may be dismissed as a causative factor. The second patient was given a total of 11 Gm. of sulfathiazole in one day. However, this patient's leukocyte count was only 10,000 (a relative leukopenia for a patient with pneumonia) even before the sulfathiazole was given. The total dose of sulfathiazole was too small and the period of administration too brief to cause the drop to 2,900 white blood cells, if one can draw any conclusions from experiences with sulfapyridine. Furthermore, a special sensitivity to sulfathiazole seemed unlikely, since the drug produced no effect on the patient's blood count when administered again in the same dose.

The observations in the foregoing cases indicate that the presence of leukopenia is no contraindication to the use of sulfapyridine in the treatment of lobar pneumonia. The rise in the white blood count after sulfapyridine administration was due to the control of the severe infection which was the cause of the original leukopenia. There have been three reports of somewhat analogous cases in which sulfanilamide was therapeutically helpful in the treatment of streptococcic infections associated with granulocytopenia due either to the infections or to the ingestion of aminopyrine. Since the presence of a low leukocyte count in patients with lobar pneumonia is usually associated with a relatively more severe infection and a higher mortality than in persons with leukocytosis, and since sulfapyridine is the most effective single therapeutic agent in the treatment of lobar pneumonia, leukopenia seems to be a special indication for the use of this drug in the therapy of lobar pneumonia.

## SUMMARY

1. The two cases of acute lobar pneumonia here reported presented severe leukopenia, the white blood cells numbering as low as 700 and 2,900 per cubic millimeter respectively.

2. In both cases, multiple lobes were involved; there was intense bacteremia, and the clinical condition was desperate despite the use of huge doses of type-specific antipneumococcus serum.

3. After the administration of sulfapyridine there was a prompt improvement in the clinical picture with a subsequent favorable course. The leukocyte count rose progressively and in one case reached 58,000 per cubic millimeter before regressing toward normal.

3. Samuels, S. S., and Lambert, R. A.: Relationship of the Leukocyte Count and Bone Marrow Changes in Acute Lobar Pneumonia, *J. Infect. Dis.* 23: 443 (Nov.) 1918.

## CONCLUSION

The presence of leukopenia in cases of acute lobar pneumonia does not contraindicate the administration of sulfapyridine. In fact, when lobar pneumonia is associated with leukopenia sulfapyridine therapy is especially indicated, because such cases usually represent severe pneumonic infections with a relatively high mortality.

1088 Park Avenue.

## SULFANILAMIDE IN THE THERAPY OF ACTINOMYCOSIS

LEONARD DOBSON, M.D.

EMILE HOLMAN, M.D.

AND

WINDSOR CUTTING, M.D.

SAN FRANCISCO

Chemotherapeutic successes in the field of bacterial and protozoal infections have not yet been equaled in the virus or fungus groups. Of the virus infections, only venereal lymphogranuloma and trachoma have seemed responsive to sulfanilamide. There have been relatively few reports of the effect of sulfanilamide in fungous infections.

Six clinical reports have mentioned the use of sulfanilamide or related compounds in actinomycosis, and one report describes a trial of the drug in an experimental infection. The earliest of these was that of Walker,<sup>1</sup> who in 1938 reported a case of abdominal actinomycosis arising from the appendix, which healed quickly after two courses of sulfanilamide. The first course lasted six days and the second five days, with an interval of ten days. The dosage was 1 Gm. three times a day throughout. Compound solution of iodine and potassium iodide had been given previously without effect.

Bailey,<sup>2</sup> also in 1938, reported a case in which potassium iodide, sodium iodide intravenously, thymol and sulfanilamide were administered. The report, made while the patient was still in the hospital, stated that he was improved but not well. The dosage of sulfanilamide was not mentioned.

Miller and Fell<sup>3</sup> reported a case in which a mass in the lower part of the abdomen of a boy proved on incision to be actinomycotic. Thymol and potassium iodide were given orally, thymol in oil applied locally, and roentgen irradiation given as well, over a period of four months. The patient lost strength and the abdominal mass grew larger, however, and sulfanilamide was started in small doses, 0.65 Gm. three times a day. This was continued for ten months with apparently complete recovery.

Ogilvie<sup>4</sup> recently reported a case of actinomycosis probably arising in the appendix and involving a large part of the anterior abdominal wall. Despite surgical opening of the sinuses and long continued administration of iodide, the infection advanced. Sulfapyridine, 2 tablets six hourly (this probably being 4 Gm. a day),

From the Departments of Surgery and Pharmacology of the Stanford University School of Medicine.

1. Walker, O.: Sulfanilamide in the Treatment of Actinomycosis, *Lancet* 1: 1219 (May 28) 1938.

2. Bailey, W. H.: A Case of Actinomycosis in Man, *J. Oklahoma M. A.* 31: 339 (Oct.) 1938.

3. Miller, E. M., and Fell, E. H.: Sulfanilamide Therapy in Actinomycosis, *J. A. M. A.* 112: 731 (Feb. 25) 1939.

4. Ogilvie, W. H.: Abdominal Actinomycosis Treated with Sulfapyridine, *Brit. M. J.* 2: 254 (Aug. 24) 1940.

was given with dramatic and permanent recovery. The drug was given for only thirteen days, average blood levels being 2 mg. per hundred cubic centimeters for the free drug and 3.3 mg. per hundred cubic centimeters for the total drug. The author suggests that the action of the drug was largely against the coincidental streptococcal infection and that the cure of the actinomycosis then resulted from natural processes.

Sudler and Johnson<sup>5</sup> recently reported two cases of actinomycosis of the jaw treated successfully with sulfanilamide. One of the patients was getting worse while on iodides and roentgen treatments and then healed promptly after two short courses of sulfanilamide. The second patient was treated with sulfanilamide alone.

Morton<sup>6</sup> reported 3 cases of actinomycosis, in 2 of which sulfanilamide was administered. In 1 there was involvement of the jaw, face, meninges and brain, and death occurred although sulfanilamide was given at one time for a period of a month in doses of 4 Gm. daily. In the other case there was actinomycosis of the breast and axilla, and sulfanilamide was given intermittently for about six weeks in doses of 4 to 8 Gm. daily, with blood levels of 4 to 8 mg. per hundred cubic centimeters. At the time of the report the patient was improved but not well. Both of these patients had iodides, roentgen rays and vaccine injections, as well as sulfanilamide, and the patient who died also had thymol applied locally.

The experimental report was that of Hemmens and Dack,<sup>7</sup> who found that they could cure otherwise fatal infections of rabbits with *Bacterium necrophorum*, an organism distantly related to *Actinomycosis bovis*, by early and persistent treatment with sulfanilamide.

These favorable reports are in considerable contrast to the conclusion of Good,<sup>8</sup> who in 1931 reported 62 cases of abdominal actinomycosis. Treatment consisted of free drainage, potassium iodide, general upbuilding and radium or roentgen irradiation. Only 8 were apparently cured, and it was concluded that the results were generally poor. More recently another report from the Mayo Clinic by Masson<sup>9</sup> included 2 cases treated with roentgen rays and small doses of iodide, with complete recovery. Mention is made of another fatal case, however.

We are reporting three cases of actinomycosis, one of the jaw, one of the chest and one of the abdomen, all completely cured, in which the administration of sulfanilamide seemed to be the deciding therapeutic agent.

#### REPORT OF CASES

CASE 1.—S. K., a barber aged 65, entered Stanford Hospital on Sept. 30, 1937 for a swollen and painful jaw of three months' duration. Two teeth in the lower jaw had been removed in July in a fruitless effort to correct the pain, followed by an increasing swelling of the right face. There was no history of contact with possible sources of mycotic infection.

Physical examination revealed an extensive swelling of the right side of the face from the temporal fossa to the submaxillary region (fig. 1 A). This swelling was quite hard except for a small area of fluctuation immediately over the malar bone. The patient was unable to open the jaw more than  $\frac{1}{8}$  inch. A roentgenogram disclosed several areas of bone destruction

of the right mandible, one area opening into the open alveolus from which the right second molar had been removed.

The Wassermann reaction was negative. The red cells numbered 3,600,000, the white cells 14,000, of which 73 per cent were neutrophils (1 per cent banded), 21 per cent lymphocytes and 6 per cent monocytes. The hemoglobin was 67 per cent of normal. The urine was normal.

On October 4 a short incision was made over the fluctuant area, evacuating a light, thin pus containing numerous grayish yellow granules. Actinomycosis was suspected and subsequently proved by studies of a smear, culture and tissue sections. A clamp introduced through the malar incision dropped into an abscess cavity around the mandible. A counter incision was made at the angle of the jaw.

Roentgen treatment to the right side of the face was administered on October 6 and 7 for a total of 500 roentgens and again on November 10 and 11 for a total of 500 roentgens. Potassium iodide was given in increasing amounts until the

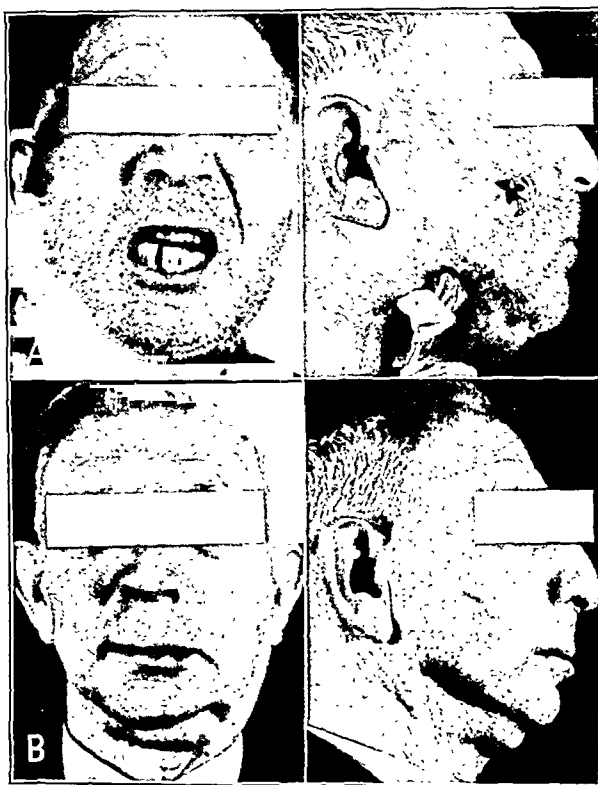


Fig. 1 (case 1).—Appearance of patient: A, Oct. 5, 1937, before treatment; B, Feb. 16, 1940, after treatment.

patient was getting 12 Gm. daily. Ferrous sulfate, halibut liver oil and brewers' yeast supplemented the diet.

Improvement was slight and on November 16, because of inadequate drainage, the previously made wounds were enlarged and connected with a spontaneously developed opening anterior to the angle of the jaw. Bare mandible was revealed in the wound. Intractable pain followed this procedure. On November 23 sulfanilamide was begun 1 Gm. every six hours, and an almost immediate reduction in pain occurred.

Within three days there was visible improvement in the wound, the redness of the skin and the induration being markedly lessened and the discharge decreased. Within ten days a sinus which had burst through the skin spontaneously only ten days before the administration of the sulfanilamide had practically healed, and the patient was sleeping without sedatives. On December 8 the sulfanilamide was discontinued. On this date there was very little discharge, induration had practically disappeared, and the patient was able to open his mouth fully 2 cm.

By December 15, induration had again set in and pus in which sulfur granules were easily demonstrated was again obtained from the wounds. Again sulfanilamide, 1 Gm. every six hours,

5. Sudler, M. T., and Johnson, C. B.: Treatment of Actinomycosis with Sulfanilamide, *J. Kansas M. Soc.* 40: 330 (Aug.) 1939.

6. Morton, H. S.: Actinomycosis, *Canad. M. A. J.* 42: 231 (March) 1940.

7. Hemmens, E. S., and Dack, G. M.: Effect of Sulfanilamide on Experimental Infections with *Bacterium Necrophorum* in Rabbits, *J. Infect. Dis.* 64: 43-48 (Jan.-Feb.) 1939.

8. Good, L. P.: Actinomycosis of the Abdomen, *Arch. Surg.* 22: 307 (Feb.) 1931.

9. Masson, D. M.: Abdominal Actinomycosis: Report of Two Cases with Clinical Cure, *Proc. Staff Meet., Mayo Clin.* 11: 833 (Dec. 30) 1936.

was administered, and on December 31 the patient was discharged from the hospital with draining sinuses but practically no swelling of the face.

Owing to a widespread dermatitis, the sulfanilamide was discontinued on January 5 and potassium iodide was again given. Small beads of pus could occasionally be expressed from the sinuses, which invariably contained a few sulfur granules. On February 15 and 16 roentgen treatments for a total of 500 roentgens were again administered, and again on May 9 and 10.

In July the patient returned with a small abscess in the temporal region from which a half ounce of pus was evacuated, but *Actinomyces* was not present. Healing was complete on Aug. 1, 1939. When last seen, in January 1940, the patient was still perfectly healed and well (fig. 1 B).

**CASE 2.**—E. Z., a student aged 24, in March 1939 felt pain in the right side of his neck and chest, which was worse on motion. Three months later, roentgen examination of the chest showed density in the right upper lobe, and a swelling appeared medial to the right scapula which on incision yielded pus containing *Actinomyces*.

On admission at this time he was referred by his physician in the Woodland Clinic to the Stanford Medical Service for further care. He was febrile and somewhat prostrated. In addition to the draining sinus near the scapula and impaired physical signs over the right upper chest, the liver and spleen were palpable. The patient was moderately anemic, with a red count of 3.5 million and a hemoglobin of 53 per cent Sahli. The white blood cell count was 10,000, with a normal differential. The urine and stool were not remarkable, the blood Wassermann reaction was negative, and the sedimentation rate was 26 mm. per hour, corrected. Roentgen examination of the chest showed density in the upper half of the right lung field (fig. 2 A).

The patient was immediately started on sulfanilamide, 6 Gm. daily, which was continued for eight days. At this time the smear from the draining sinus had become negative for *Actinomyces*, and the patient felt better, but his temperature, which had receded to normal, again rose. For this reason the sulfanilamide was reduced to 4 Gm. daily for two days, then discontinued for three days. Six Gm. daily was then given for another week. Sodium iodide was given during the next month in increasing doses until he was taking 4 Gm. daily. In the meantime he was treated generally with a high calory diet, vitamins, ferrous sulfate and three transfusions. The sinus stopped draining entirely two weeks after the sulfanilamide was stopped, and one month later the patient was dismissed, apparently nearly well, although the roentgen appearances in the right upper lung field were little changed. His hemoglobin at this time was 78

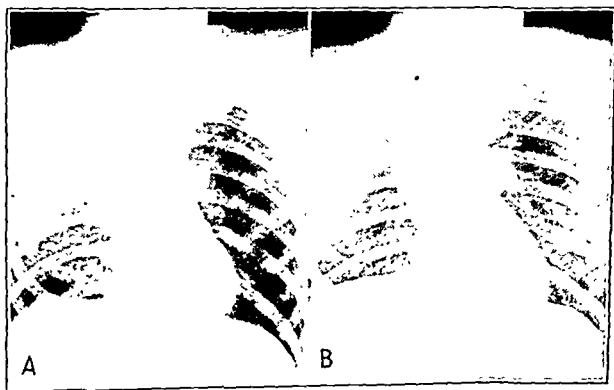


Fig. 2 (case 2).—A, density in the upper half of the right lung field, June 5, 1939; B, decrease in the density, Dec. 14, 1939.

per cent Sahli, his white blood cell count 8,700, and sedimentation rate 20 mm. per hour, corrected. He was seen at intervals thereafter, five months later feeling well, with a sedimentation rate of 7 mm. per hour, and with roentgen evidence of only a little density in the right lung (fig. 2 B). The last report, a year after the onset of the infection, states that he seemed entirely well.

**CASE 3.**—A 12 year old Japanese schoolboy bumped the lower right part of his abdomen on the corner of a table on Nov. 10,

1939. The area continued to be tender and on December 1 a hard lump could be felt beneath the lower right rectus muscle. The possibility of a subfascial hematoma was considered by his local physician, Dr. George R. Sasaki, of Salinas, Calif., but a diagnostic puncture obtained no blood or pus from the mass. On December 8 Dr. Sasaki made an incision along the lateral



Fig. 3 (case 3).—Section showing ray fungi; reduced from a photomicrograph with a magnification of 100 diameters.

border of the rectus muscle exposing a large, firm mass which contained small areas of necrosis. Microscopic examination (fig. 3) by Dr. James B. McNaught, of the Stanford Department of Pathology, showed the tissue to contain the ray fungus of actinomycosis. Iodides were started but the wound continued to drain thick yellow pus. On December 17 the boy developed a marked cystitis. On December 21 he was brought to Stanford Hospital.

On admission he was pale and weak. The abdomen showed thick yellow pus draining from two granulating sinuses near the center of a lower right rectus scar (fig. 4 A). On palpation there was a stony hard, tender, fixed mass in the right lower quadrant measuring 9 by 7 cm. On rectal examination a tender mass could be felt anteriorly which largely filled the pelvis.

The laboratory studies showed a slight secondary anemia with 4,640,000 red blood cells with 80 per cent hemoglobin, and 18,400 leukocytes with 80 per cent polymorphonuclears, 3 per cent eosinophils and 17 per cent lymphocytes. The urine showed a heavy cloud of albumin with a few red blood cells and 40 to 50 leukocytes per high power field.

Sulfanilamide was immediately started, beginning with 0.5 Gm. every four hours, with sodium bicarbonate 0.5 Gm. every four hours. On the following day the dose of sulfanilamide was increased to 0.75 Gm. every four hours (total 4.5 Gm. daily). A blood sulfanilamide determination on the day following admission, December 22, showed free blood sulfanilamide to be 4.0 mg. per hundred cubic centimeters and total 5.6 mg. On December 23 free blood sulfanilamide was 8.2 mg. per hundred cubic centimeters, total 10.4 mg., and on December 24 free blood sulfanilamide was 9.2 mg. per hundred cubic centimeters and total 11.4 mg., as included in figure 5.

The cystitis subsided rapidly after the sulfanilamide was started. Within twenty-four hours the marked frequency and burning on urination had decreased and within forty-eight hours the urine was practically clear. The drainage from the abdominal sinuses diminished rapidly and within one week the abdominal mass was measurably smaller. On Jan. 3, 1940, an abscess pointing at the umbilicus was incised and drained. The pus contained long filamentous branching gram-positive rods and typical sulfur granules. By January 10 the pelvic mass, which had been felt by rectum, was no longer palpable.

The hemoglobin dropped from 80 per cent to 65 per cent on December 29. The temperature, which on admission was 37.8 C. (100 F.) rectally, started to rise on December 26 and rose to

39.8 C. (103.6 F.) on December 29. It was felt that the high fever may have been due to the effect of the sulfanilamide, so it was discontinued on December 29. The temperature came down promptly with no other change in therapy and became normal

within twenty-four hours. On Jan. 2, 1940, four days after the sulfanilamide was stopped, the hemoglobin had risen to 69 per cent. On January 2 the sulfanilamide was again started, 0.75 Gm. being given every four hours, and this dose was continued until January 16, when the dose was dropped to 0.5 Gm. every four hours.

The abdominal mass slowly decreased in size and the drainage lessened between December 21 and January 7 and then for several days seemed about stationary. On January 12, sodium iodide was started, 1 Gm. being given three times daily. On January 13, roentgen treatment was started, eleven treatments of 50 roentgens each being directed to the right lower part of the abdomen (January 13, 20, 27, 31, February 3, 6, 10, 14, 17, 21, 24 to a total of 715 roentgens).

The sodium iodide was administered for two days. On the second day the patient again started having a fever; the temperature reached 39 C. (102.2 F.). This febrile reaction was believed to be due to the sudden liberation of toxic material from the abscess from the action of the sodium iodide, so the iodide was stopped. On February 8, sodium iodide was again started, gradually being increased to 1 Gm. three times daily, which was continued throughout his stay in the hospital.

Additional therapy included a high caloric, high-vitamin diet and 0.2 Gm. of ferrous sulfate four times daily. On this regimen the mass continued to diminish in size, the sinuses healed and the patient's appetite and strength increased. The blood count improved, rising to 87 per cent hemoglobin before the patient's dismissal. He also gained 10 pounds (4.5 Kg.) during his stay in the hospital. On dismissal on March 21, three months after admission, there was no mass palpable in the abdomen.

The patient was kept on sulfanilamide 0.5 Gm. every four hours and 1 Gm. sodium iodide daily for one month after dismissal. Two months after dismissal a small furuncle developed in the scar, and although it appeared to be superficial it was decided to start sulfanilamide again. The patient was put on 0.3 Gm. of sulfanilamide four times daily and 1 Gm. of sodium iodide three times daily. This dosage was continued for another month. Within three days the infection had healed. The patient was last seen on Dec. 20, 1940, ten months after dismissal. He was well and there was no evidence of residual actinomycosis (fig. 4B). The clinical course is summarized in figure 5.

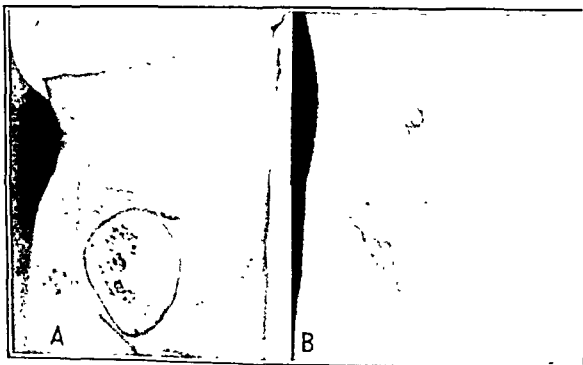


Fig. 4 (case 3).—Abdomen: A, Dec. 22, 1939, before treatment; B, Sept. 24, 1940, after treatment.

#### COMMENT

The cases reported detail the apparently complete cures of a man with actinomycosis of the jaw, another with involvement of the lung and rib cage, and a boy with serious and extensive abdominal actinomycosis. Sulfanilamide was used in all three cases.

Although it has been suggested that the effect of sulfanilamide is merely to combat secondary invaders

in the abscesses and sinuses, allowing the natural bodily resistance to overcome the fungus, the rapid and complete recoveries reported in the literature and the striking responses in our cases suggest that there may be a direct effect as well. This view is to some extent

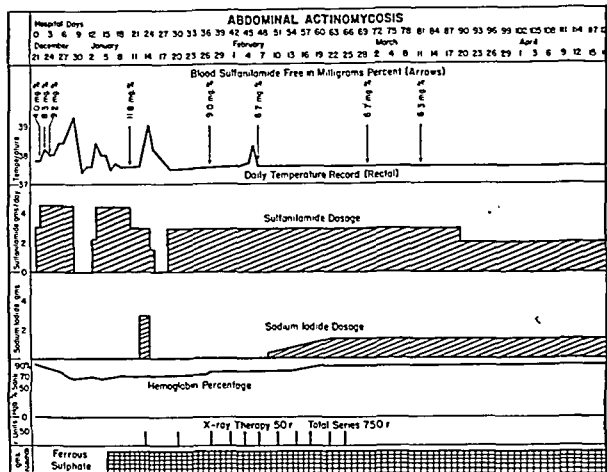


Fig. 5 (case 3).—Clinical course while patient was under treatment.

supplemented by the reported effectiveness of sulfanilamide on an experimental infection with an organism related to *Actinomyces bovis*. However, in our case of abdominal actinomycosis the lesion remained roughly stationary after about a month of treatment with sulfanilamide and then regressed completely after further sulfanilamide and the addition of iodides and roentgen rays. This suggests that the principal effect during the early stages of treatment was on the secondary invaders and that other factors were important in the final cure. It is impossible to be definite on this point in the absence of *in vitro* studies or experimental pure culture infections.

There are several incidental points of interest. Over the first two weeks of the sulfanilamide course in case 3 there was a gradually progressing secondary anemia. Despite continuance of the sulfanilamide, and perhaps aided by the ferrous sulfate, this disappeared, so that the hemoglobin was normal on the patient's dismissal. It is reassuring to know that the slow anemia can, at least at times, be completely controlled while the drug is still being administered. Adaptation of the blood forming system to the drug may well have been more important than the iron therapy. Two of the patients had what was interpreted as episodes of drug fever, yet therapy was continued after short intermissions without untoward results. Another spike of fever coincided with the abrupt administration of a large dose of sodium iodide (3 Gm. daily) and possibly was due to absorption of liquefied toxic substances from the granuloma. When repeated later in smaller, ascending doses, there was no recurrence of this toxic sign.

#### CONCLUSIONS

Three cases of actinomycosis, one of the jaw, one of the lungs and rib cage, and one of the abdomen, have been apparently completely cured. Therapy included the use of sulfanilamide, iodides and roentgen rays. In view of the serious nature of this infection and the apparent value of sulfanilamide, this or a related drug should be included in the treatment of actinomycosis.

Sacramento and Webster streets.

## THE CHEMOTHERAPY OF GONOCOCCIC INFECTIONS

### I. SUMMARY OF EXPERIENCE WITH SULFANILAMIDE

### II. INVESTIGATION OF CHEMOTHERAPEUTIC EFFECT OF SULFAPYRIDINE

C. J. VAN SLYKE, M.D.

R. R. WOLCOTT, M.D.  
AND

J. F. MAHONEY, M.D.

Passed Assistant Surgeon, Passed Assistant Surgeon and Senior Surgeon, Respectively, United States Public Health Service

STATEN ISLAND, N. Y.

Previous reports by us<sup>1</sup> have presented the results of studies dealing with the use of sulfanilamide in the treatment of gonococcic infections. In the present paper it is desired to set forth the results of a similar investigation of sulfapyridine and to compare the adaptability of sulfanilamide and sulfapyridine therapy to the treatment needs of the disease.

### I. SUMMARY OF EXPERIENCE WITH SULFANILAMIDE

Our efforts during 1937 and 1938 were concentrated on studies of sulfanilamide therapy in gonococcic infections of approximately 1,800 hospitalized male and female patients. Under ideal conditions sulfanilamide proved to be a valuable agent in the treatment of this disease. By means of large doses (1.3 Gm.) of sulfanilamide given at four hour intervals during both day and night, it was possible to effect a high percentage of cures. Although serious toxic effects did not occur in the series, it is well recognized that the character of toxic manifestations restricted full therapeutic dosages of sulfanilamide, especially in outpatients, and consequently lessened its value as a means of reducing significantly the incidence of the disease. From the information gained from that series, which was reported previously, the following conclusions were drawn:

1. When consideration is given to the duration of the infection there is little if any difference in the curative response of male or female patients.

2. Higher blood concentrations of free sulfanilamide approximating 9 to 11 mg. per hundred cubic centimeters appear to be more effective in producing cures than lower levels of 3 to 6 mg. per hundred cubic centimeters. Cures and failures occur at both levels, however.

3. The exaggeration of the toxic manifestations occasioned by the large doses necessary to produce and maintain the higher concentration in the blood suggests the advisability of hospitalization at least during the period of intensive therapy.

4. Prolonged administration of sulfanilamide is contraindicated. If a favorable therapeutic response is not obtained by the fifth or sixth day, it is not likely to occur. Even with a curative response it is not advisable to continue sulfanilamide beyond the tenth or twelfth

day. The prolonged administration even of small doses of sulfanilamide appears to act as the etiologic factor in the production of granulocytopenia.

5. If sulfanilamide is given early in the course of gonorrhea, if it is given in small doses or, particularly, if given both early and in small doses it is productive of a low cure rate and apparently establishes in many failures a condition simulating a "sulfanilamide resistant" infection.

6. A febrile response of 100.8 F. or over, occasioned by sulfanilamide therapy, is an indication to suspend or decrease the amount of sulfanilamide.

7. The dosage of sulfanilamide cannot be routinized. Adequate dosage of the individual patient should be decided daily on the basis of laboratory findings and sound clinical judgment.

8. Sulfanilamide is capable of producing a subclinical state of gonococcic infection in which, for a time, the disease may be completely asymptomatic and which may be detected only by finding the gonococcus on spread or culture examination. Prolonged observation of the patient is important, especially where reliable cultural investigations are not freely accessible.

9. Sulfanilamide is a powerful chemotherapeutic agent which should be used only under continuous and competent medical supervision.

10. An immune mechanism may be essential for the most efficient action of sulfanilamide. This hypothesis receives support from the fact that the cure rate increases when sulfanilamide treatment is delayed. This result is portrayed graphically in the accompanying charts.

### II. INVESTIGATION OF CHEMOTHERAPEUTIC EFFECT OF SULFAPYRIDINE

*Material.*—In a series of 300 cases under report, there are 200 male and 10 female patients who were hospitalized and 81 men and 9 women who were treated as outpatients. Not any of the hospitalized or outpatient women had had previous chemotherapy. Among the men, however, there were 136 inpatients and 30 outpatients who had been treated elsewhere and had failed to respond to one or more therapeutic attempts with sulfanilamide or allied compounds. The series is representative of routine admissions, selection not being exercised. Every patient had an obvious gonococcic infection which was confirmed by spread and culture methods before sulfapyridine therapy was started.

*Routine Procedure.*—The 200 male patients who were hospitalized received the usual clinical and laboratory examinations and hospital care. They were not confined to bed. For a time the fluid intake was restricted to 1,500 cc. a day, but this limitation was later abandoned as nonessential. Sulfapyridine was administered at four hour intervals night and day. Daily spreads and two glass urine tests were carried out. The carbon dioxide combining power of the blood plasma was followed in 27 patients. On complete relief of symptoms, negative findings in spreads, cessation of discharge and clearing of the two glass urine test, a moderately sized urethral sound was passed and the penile urethra massaged. The resulting material, together with that secured from prostatic massage, was subjected to spread and culture examination. The spread and culture studies were repeated on an average of more than six occasions. Concentration and excretion studies in the present series, as well as those

From the Venereal Disease Research Laboratory.

1. Van Slyke, C. J.; Thayer, J. D. and Mahoney, J. F.: Sulfanilamide Therapy in Gonococcal Infections, *Ven. Dis. Inform.* 18: 417, 1937. Mahoney, J. F.; Van Slyke, C. J. and Thayer, J. D.: Sulfanilamide in Hospitalized Gonorrhea, *Am. J. Syph., Gonorr. & Ven. Dis.* 22: 691, 1938. Van Slyke, C. J. and Mahoney, J. F.: Further Observations in Sulfanilamide Therapy of Gonococcal Infections, *New York State J. Med.* 40: 122, 1940. Nimelman, Anna; Mahoney, J. F., and Van Slyke, C. J.: Sulfanilamide Therapy of Gonococcal Infection in Hospitalized Prostitutes: The Gonococcus and Gonococcal Infection, *New York, Science Press*, 1939, p. 132.



reported by Long and Feinstone,<sup>2</sup> have shown that sulfapyridine is not demonstrable in the body fluids at the end of three or four days. Therefore a special effort was made to secure as many culture studies as possible beginning five days after the discontinuance of medication, in order to obviate the possible inhibiting influence of sulfapyridine on the growth of gonococci in cultures.

If repeated physical examinations, two glass urine tests and spread and culture studies failed to reveal evidence of residual gonococcic infection, the patient was considered apparently cured and discharged from the hospital. All were advised to return at frequent intervals for posttreatment observation and to reenter the hospital in the event of recurring symptoms. Sexual intercourse with the protection of a condom, or the moderate use of alcoholic beverages, was not interdicted. Satisfactory clinical response and repeated failure to demonstrate the causative organism in material obtained by urethral and prostatic massage constituted the essential criteria of apparent cure.

The 10 female patients who were hospitalized received comparable care, except that sulfapyridine in smaller doses was given only four times a day at four hour intervals. The criteria of apparent cure in hospitalized women demanded:

1. Disappearance of purulent discharge from the urethra and cervix, together with cessation of clinical evidence of specific infection.
2. Evidence of satisfactory recession of adnexal involvement.
3. Negative findings in repeated spread and culture examinations.

The 81 male and 9 female patients who received sulfapyridine on an outpatient basis were likewise subjected to prolonged spread and culture studies in addition to urinalyses, hemoglobin determinations, white cell counts and determinations of free and total blood sulfapyridine. Usually these patients were seen three times during the first week, twice during the second week and then weekly thereafter. They were instructed to take sulfapyridine four times daily at four hour intervals, i. e., at 8 a. m., 12 noon, 4 p. m. and 8 p. m. The criteria of cure were the same as stated for the hospitalized patients, and a minimum of three negative

Douglas chocolate agar and the Difco medium for gonococci were inoculated. Incubation was carried out at 35 C. under an atmospheric tension of 10 per cent carbon dioxide. The plates were inspected at the expiration of forty-eight hours. The oxidase reaction was employed as a partial confirmatory procedure, but differentiation in questionable instances was based on the fermentation reactions. The staining method of Gram as recommended by Carpenter<sup>3</sup> was followed.

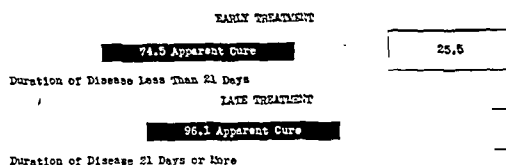


Chart 2.—Apparent rates of cure in early and late treatment (342 cases, 219 men and 123 women).

**Dosage.**—The usual dosage for the 200 hospitalized men was 6 Gm. a day for two days and 3 Gm. a day for an additional four to six days. The daily dosage was given in equally divided amounts at four hour intervals.

The usual dosage for all outpatients and for the hospitalized women was 3 Gm. for the first day and

TABLE 1.—Patient Groups and Dosage Employed

Number of Patients	Usual Dosage	Maximum Total Dosage	Minimum Total Dosage
Hospitalized men.....200	6.0 Gm. 2 days 3.0 Gm. 4-6 days	57.0 Gm. in 12 days (failure)	16.5 Gm. in 5 days (cure)
Hospitalized women.... 10	3.0 Gm. 1 day	33.0 Gm. in 10 days (failure)	10.0 Gm. in 3 days (cure)
Outpatient women..... 9	2.0 Gm. 6-9 days		
Outpatient men..... 81			

2 Gm. daily for an additional six to nine days. The daily dosage for the outpatients and hospitalized women was prescribed in four equally divided doses to be taken only during the day.

The various groups considered and the respective dosages employed are given in table 1.

**Results of Sulfapyridine Therapy.**—Of the 136 patients who had previously failed to respond to doses of sulfanilamide (administered for one or more therapeutic attempts), 103, or 75.7 per cent, were provisionally discharged as cured. Of this group 6 had also failed to be cured after two to six sessions of induced hyperpyrexia and 4 had failed to benefit from the administration of sulfanilyl-sulfanilamide (di-sulfanilamide).

Fifty-six, or 87.5 per cent, of the 64 hospitalized male patients who had not received chemotherapy before the institution of sulfapyridine treatment were discharged as apparently cured.

Nine of the 10 women who were hospitalized attained clinical and bacteriologic cures. The 1 in whom failure occurred was intolerant of the drug and received only 1.5 Gm. during a period of eight hours. This amount, however, quickly relieved the severe abdominal pain produced by an extension of the infection.

Of the 81 outpatient men, 10 lapsed treatment before completing medication or a suitable period of post-treatment observation and were not considered in

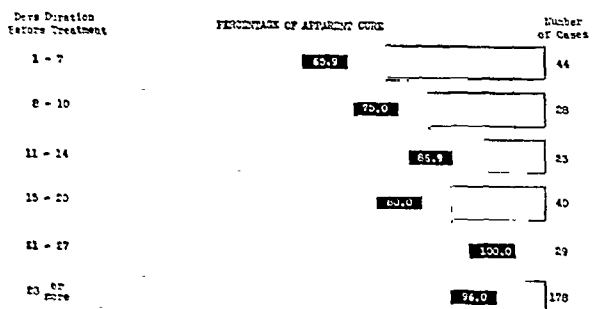


Chart 1.—Apparent rate of cure and duration of disease (342 cases, 219 men and 123 women).

cultures was obtained. It has been possible to follow some of these patients through as many as fifteen culture examinations.

**Bacteriologic Methods.**—Urethral, prostatic and cervical secretions were collected in carrying tubes of Torrey and Buckell's C medium, from which plates of both

2. Long, P. H., and Feinstone, H. W.: Observations upon the Absorption and Excretion of Sulfapyridine (2-Sulfanilyl Aminopyridine), *Proc. Soc. Exper. Biol. & Med.* 59: 486, 1938.

3. Carpenter, C. M.: Report of Laboratory and Research Committee, *Tr. Am. Neisserian M. Soc.*, 1936, p. 55.

determining the cure rate. Prior to the lapse it was noted that each of these patients received an immediate favorable therapeutic response which seemed to indicate a successful outcome, particularly since a definite failure is usually apparent after five or six days of medication.

The remaining 71 patients of this group of outpatient men are divided into two sections. One section of 29 patients had failed previously to respond to sulfanilamide therapy, but 20, or 68.9 per cent, of these satisfactorily answered the proofs of cure following sulfapyridine treatment. In the second section of 42 patients who had not received previous chemotherapy 36, or 85.7 per cent, satisfied the criteria of cure.

Cures were obtained in all 9 female patients who received sulfapyridine as outpatients.

Because of the lower cure rate secured by the use of sulfapyridine in those cases which had previously failed to respond to sulfanilamide or allied compounds, a gross cure rate is not considered, as it would naturally vary depending on the percentage of sulfanilamide failures in the group.

TABLE 2.—Results of Sulfapyridine Therapy in Gonococcic Infections

Number of Patients	Dosage	Previous Sulfanilamide		Per-centage	No Previous Sulfanilamide		Per-centage
		Therapy	Num-ber Cured		Therapy	Num-ber Cured	
Hospitalized men..... 200	6 Gm.-2 days	136	103	75.7	64	56	87.5
	3 Gm.-4-6 days						
Hospitalized women..... 10	3 Gm.-1 day	None	...	...	10	9	90.0
	2 Gm.-6-9 days						
Outpatient women..... 9	3 Gm.-1 day	None	...	...	9	9	100.0
	2 Gm.-6-9 days						
Outpatient men..... 71	3 Gm.-1 day	29	20	68.9	42	36	85.7
	2 Gm.-6-9 days						
Total..... 290		165	123	74.5	125	110	88.0

The duration of the disease before institution of sulfapyridine therapy apparently did not influence the effectiveness of the treatment.

The male patients who responded favorably experienced rapid subsidence of symptoms and disappearance or decrease of the urethral discharge to a slight amount of meatal moisture within an average of two and five-tenths days. Urethral spreads became negative for gonococci within an average of one and four-tenths days, but it was not exceptional to find occasional extra-cellular gram-negative diplococci in a few subsequent examinations.

The bacteriologic response and relief of subjective symptoms was equally good in women, although the objective symptoms of the infection disappeared somewhat more slowly.

Practically all the patients who failed to satisfy the criteria of cure displayed an initial response consisting of decrease of discharge and lessening of subjective symptoms. Although the clinical improvement continued in a portion of this group, there were always sufficient clinical signs to warn of the presence of the infection within six days after discontinuance of medication. There was not any instance of extension of the disease during treatment, even among the failures. No common factor was discernible to which the failures could be attributed.

Table 2 summarizes the results of sulfapyridine therapy in gonococcic infections.

*Results in Complicated Cases.*—There did not appear to be any appreciable difference in the response of complications of gonococcic infections between the hospitalized patients who received the larger doses of sulfapyridine and the outpatients who received the smaller doses.

Unilateral epididymitis was observed in 4 hospitalized and 2 outpatients. In each case the pain was entirely relieved within twenty-four to thirty-six hours and the swelling subsided within three to ten days.

Two cases of acute gonococcic arthritis were observed in the hospitalized group. One man displayed redness and swelling of the wrist and ankle, which was accompanied by severe pain. The pain was entirely relieved in five days, the swelling disappeared and complete physiologic function was restored within an additional five days. The other experienced intense pain and effusion of the knee joint. Under sulfapyridine therapy the pain was relieved on the second day and the knee, aided by radiant heat, became normal by the eleventh day.

Acute pelvic inflammatory disease, causing moderate to severe pain, was seen in 6 of the 19 female patients. In 5 the pain was completely relieved within one to three days. The sixth patient was also immediately relieved, although she was intolerant of the drug and received only 1.5 Gm. within an eight hour period. Amelioration of the severe pain of acute adnexal involvement was consistent, striking and rapid.

*Toxic Manifestations.*—Even with the larger doses (6.0 Gm. a day) administered to the hospitalized group of patients, toxic manifestations were encountered less frequently and appeared to be less severe during treatment with sulfapyridine than with sulfanilamide. The patients receiving the smaller doses of sulfapyridine almost uniformly evidenced less toxic symptoms, and these of a milder character, than did those patients who were given the larger amounts. For this reason the tabulation of toxic manifestations (table 3) is divided into two groups.

Many of the toxic manifestations recorded were elicited only by recounting the possible symptoms. The probability of suggestion provoking an affirmative reply is not subject to a statistical analysis in this instance.

Most of the toxic symptoms noted in table 3 occurred for a day or two early in the course of treatment. In only 1 instance in the outpatient group was sulfapyridine intolerance pronounced enough to demand discontinuance of therapy.

It is not possible to offer data on the incidence of fever produced by sulfapyridine therapy in the outpatient group, but in the 210 hospitalized patients, in whom the temperature was recorded every four hours, only 1 patient developed a temperature of more than 37.6 C. (101.1 F.). In this man a temperature of 38.4 C. was noted on only a single day, the twelfth day of medication.

There was not any evidence which indicated that the production of toxic manifestations caused permanent ill effects.

*Correlation of Therapeutic Response, Clinical Course and Laboratory Studies.*—The results of the laboratory studies, outlined in an earlier statement, and their correlation with clinical experience may be summarized as follows:

1. The absorption of sulfapyridine was irregular and could be determined only by studies of the blood concentration.

2. The amount of acetylated sulfapyridine in the blood varied widely and offered no explanation for differences noted in toxic or treatment responses.

3. Constant blood levels of sulfapyridine in individuals on unchanged daily doses were not appreciably altered by fluid intakes up to 5,000 cc. a day. Therefore the initial restriction of fluid intake was abandoned.

4. Blood concentrations of 2 or 3 mg. per hundred cubic centimeters or less appeared sufficient for patients whose gonococcic infections were amenable to sulfapyridine therapy. The cure rate evidenced by the patients who had 5 to 14 mg. per hundred cubic centimeters of free sulfapyridine in the blood was approximately equal to the cure rate obtained in those in whom the blood level was below 5 mg. per hundred cubic centimeters.

5. In contradistinction to the results with sulfanilamide, there was not any clinical evidence of acidosis, nor was there a decrease in the carbon dioxide combining power of the plasma as determined in 27 cases studied.

6. There were not any instances of acute hemolytic anemia. There was a slight decrease in hemoglobin content in approximately one half of the patients under report. The remainder showed either no change or a slight increase in the content of hemoglobin while under treatment.

7. There were not any cases of granulocytopenia. Almost all of the patients had a slight elevation of the white cell count at the beginning of treatment, followed by a depression in the number of white cells to a level of 5,000 to 7,000 per cubic millimeter. Many of the patients showed temporary drops to counts between 4,000 and 5,000 cells per cubic millimeter. The cell count fell to 3,700 in only one instance but returned to a higher level on subsequent examinations without discontinuance of therapy. Differential cell counts showed a slight but uniform tendency toward monocytosis, reaching a maximum of 19 per cent in one case.

8. Hematuria was not found either by gross inspection or by the benzidine test. The dark color of some urines (negative by microscopic and benzidine tests for blood) suggested the presence of hematoporphyrin. The change in color of the urine did not interfere with routine treatment and disappeared after termination of the drug. Hematoporphyrinuria was not ascertained definitely because of a lack of suitable apparatus for precise spectroscopic examinations. There were not any symptoms suggestive of renal colic.

#### COMMENT

From the practical point of view resulting from experience in treating 300 cases of gonococcic infection and the recorded results of twenty-two authors who treated 1,745 similar cases, it is evident that blood concentration studies have a limited clinical application in sulfapyridine therapy. It is also evident from the total lack of major toxic manifestations noted in this large collective group that blood counts, hemoglobin determinations and urinalyses may be dispensed with if the lack of laboratory facilities would otherwise curtail the use of the drug.

In the general management of the patients it was not found necessary to restrict any article of diet or to interdict any ordinary daily activity. The patients were cautioned concerning sexual excitement and the use of alcoholic beverages. However, a few of the outpatients continued to indulge in alcohol more or less freely dur-

ing and subsequent to the administration of sulfapyridine; a lessening of the general cure rate in these patients was not noted.

As previously mentioned, the passage of sounds and prostatic massage became a routine procedure as soon as clinical and microscopic evidences of the disease were absent. This procedure was usually started on the fourth or fifth day after initiation of medication. Among the cases reported in this paper, in the treatment of which either sulfanilamide or sulfapyridine had been used and in which the demands of clinical cure and spread negativity had been satisfied, there was not a single instance of extension of the disease attributable to the practice. The passage of sounds and the prostatic massage on the fourth or fifth day of treatment may be regarded by some as therapeutic heresy, but if the precautions outlined are observed it is believed that these measures are not only harmless but actually enhance the cure rate by promoting early and adequate urethral drainage.

TABLE 3.—Toxic Manifestations Resulting from Sulfapyridine Therapy

Toxic Manifestation	200 Hospitalized Men			100 (10 Hospitalized Women) (9 Outpatient Women) (81 Outpatient Men)		
	Sulfapyridine 6.0 Gm. 2 Days 3.0 Gm. 4-6 Days			Sulfapyridine 3.0 Gm. 1 Day 2.0 Gm. 6-9 Days		
	Slight, %	Moderate, %	Severe, %	Slight, %	Moderate, %	Severe, %
Nausea.....	27.0	25.5	4.5	28.0	4.0	1.0
Vomiting.....	13.0	4.0	2.0	7.0	3.0	...
Headache.....	34.5	20.5	1.5	32.0	5.0	3.0
Vertigo.....	29.0	7.5	...	19.0	1.0	...
Weakness.....	4.5	13.5	...	6.0	2.0	...
Anorexia.....	16.5	7.0	...	11.0	4.0	...
Insomnia.....	11.5	4.5	...	7.0	4.0	...
Dermatitis.....	7.5	2.0	...	5.0	1.0	...
Cyanosis.....	2.5	1.0	...	3.0	...	...
Nervousness.....	...	0.5	...	3.0	...	...
Chilliness.....	...	0.5	...	...	...	...
Backache.....	1.5	1.0	...	4.0	...	...
Palpitation.....	...	0.5	...	2.0	...	...
Pruritus.....	...	...	...	1.0	...	...
No toxic effect.....	10% of patients			29% of patients		

A few patients who failed on a first course of sulfapyridine and were therefore listed as failures obtained apparent cures following two or three weeks of rest or local therapy and a subsequent exhibition of the drug. A cure was effected in approximately two thirds of the group. These were, however, not included in the statistical analysis because (1) a second course of sulfapyridine was given in only a portion of the failures and (2) in the series under report primary interest has been to determine the ability of sulfapyridine to produce a successful outcome as a result of one course of administration. For the latter reason investigations have not been conducted concerning the advisability of concomitant local treatment. The literature reviewed suggested that a combination of local treatment with the oral administration of sulfapyridine generally added little if anything to the basic cure rate.

It has been previously mentioned that in persons failing to be cured of their gonococcic infections by sulfapyridine there was ample clinical evidence of the presence of the infection within six days of the discontinuance of medication. In discussing this point Herrold<sup>4</sup> also found that, "when cure was not effected

4. Herrold, R. D.: Comparative Efficacy of Sulfanilamide and Sulfapyridine in the Treatment of Gonococcal Infection. The Gonococcus and Gonococcal Infection, New York, Science Press, 1939, p. 140.

by one course of sulfapyridine, clinical exacerbation usually followed three to six days after the discontinuance of the drug."

The lack of a subclinical state is an important finding and is in contradistinction to our experience in the use of sulfanilamide, wherein a proportion of the failures were recorded as having asymptomatic infections which were elicited only by the finding of gonococci in cultures of urethral and/or prostatic secretions. Consequently when sulfapyridine is employed the absence of a subclinical, asymptomatic carrier state appears to minimize the necessity of prolonged observation and cultural studies as tests of cure.

Although the optimum time for administering sulfapyridine has not been definitely demonstrated, it appears from the results of the series under report and from the recorded data of many other investigators that sulfapyridine is as efficacious in very early acute cases as in infections of longer duration. The use of sulfapyridine in very early cases would appear, therefore, to aid materially in lessening the period of infectiousness without introducing a deleterious effect on the gross cure rate.

Both large and small dosages of sulfapyridine having been experimented with and the cure rates and the incidence and degree of toxic manifestations from each having been compared, it has become evident that the smaller doses, as prescribed for the outpatient group, are equally efficacious and considerably less toxic. It is also evident that the administration of sulfapyridine need occupy only the waking hours and need not be continued beyond seven to ten days. This means that the members of outpatient groups are able to continue their normal life with the obvious exceptions of indulgence in alcohol and sexual activity.

At the present time sulfapyridine appears to be the type of drug which can be applied on a broad basis to the control of gonococcal infections.

#### SUMMARY AND CONCLUSIONS

1. There are obvious objections to the general use of sulfanilamide as an agent in the treatment of gonococcal infection.
2. Sulfapyridine was used in 300 cases of gonococcal infection. The cure rate approximated 85 per cent for patients who had not received previous chemotherapy and 70 per cent for those who had failed to benefit by earlier sulfanilamide treatment.
3. Subclinical carrier states were not encountered among patients treated with sulfapyridine.
4. The larger dosages (6 Gm. a day) were not more efficacious than the smaller ones (2 Gm. a day).
5. Toxic responses were encountered less frequently and in milder degrees in patients receiving the smaller doses.
6. Toxic manifestations were not serious and were significantly less than with sulfanilamide.
7. Prolonged administration is not indicated. Sulfapyridine therapy should be limited to a span of ten days or less.
8. Sound clinical judgment alone may serve as a practical guide for the use of sulfapyridine in the treatment of gonococcal infection, if the lack of laboratory facilities would otherwise curtail the use of the drug.
9. Sulfapyridine therapy appears applicable to the comprehensive treatment needs of the disease.

## DIFFUSION OF SULFONAMIDE COMPOUNDS INTO THE HUMAN PERICARDIUM

MORRIS H. NATHANSON, M.D.

LOS ANGELES

With the introduction of methods for the estimation of sulfonamide compounds in blood and tissue, it was soon found that these compounds passed readily into most body tissue and fluids.<sup>1</sup> Observations have been made on saliva, milk, pleural fluid, spinal fluid, skin and sweat, bile, pancreatic juice, synovial fluid, placental blood and urine. With the exception of urine and spinal fluid, observations have not been extensive and there is still considerable information lacking concerning the distribution pattern of the various sulfonamide compounds in the body.

Long and Bliss<sup>2</sup> state that in the case of sulfanilamide the level in most body fluids is from 10 to 25 per cent lower than in the blood. Sulfanilamide is apparently more diffusible than sulfapyridine or sulfathiazole.

Long and Finestone<sup>3</sup> observed that sulfapyridine passed over into the spinal fluid in from one half to three fourths of the concentration which exists in the blood. It was found in pleural fluids in concentrations of about 75 per cent of that which was present in the blood.

Spink and Hansen,<sup>4</sup> in their clinical studies with sulfathiazole, found that this compound does not readily pass into spinal fluid. A survey of the literature fails to reveal any reference to the diffusion of sulfonamide compounds into the pericardial sac.

Observations have been made which indicate that the pericardial sac may be a relatively impermeable membrane. Drinker and Field<sup>5</sup> found that rabbit serum and horse serum are absorbed very slowly from the pericardial sac. Graphite particles of bacterial dimensions are removed very slowly and then only after phagocytosis. They concluded that the lymphatics in the basal portion of the pericardium are the principal source of drainage for these particles.

Stewart and his associates state<sup>6</sup> that they were unable to find observations relating to absorption from the human pericardial cavity. In a patient suffering from a chronic recurrent pericardial effusion of unknown etiology they found that a dye of the molecular order of phenolsulfonphthalein entered the blood stream readily from the pericardial cavity. Larger molecules, however, such as those of vital red, were not absorbed to any appreciable extent, and the dye was present in fluid removed a month later. Both dyes when injected intravenously failed to appear in the pericardial fluid.

This evidence of relative impermeability of pericardial membrane suggested a study of the diffusibility of

From the University of Southern California School of Medicine and the Medical Service, Cedars of Lebanon Hospital.

1. Marshall, E. K., Jr.; Emerson, Kendall, and Cutting, W. C.: Para-Aminobenzenesulfonamide, *J. A. M. A.* **108**: 952 (March 20) 1937.

2. Long, P. H., and Bliss, Eleanor A.: *The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds*, New York: Macmillan Company, 1939, p. 73.

3. Long, P. H., and Finestone, W. H.: *Observations on the Absorption and Excretion of Sulfapyridine*, *Proc. Soc. Exper. Biol. & Med.* **28**: 486 (Dec.) 1938.

4. Spink, W. W., and Hansen, A. E.: Sulfathiazole, *J. A. M. A.* **115**: 840 (Sept. 7) 1940.

5. Drinker, C. K., and Field, M. E.: Absorption from the Pericardial Cavity, *J. Exper. Med.* **53**: 14 (Jan.) 1931.

6. Stewart, H. J.; Crane, N. F., and Dietrick, J. E.: Absorption from the Pericardial Cavity of Man, *Am. Heart J.* **16**: 198 (Aug.) 1938.

sulfonamide compounds into the pericardial sac. Two patients with chronic pericardial effusion were available for this study:

## REPORT OF CASES

CASE 1.—H. O., a white man aged 52, was first admitted to the medical service on Nov. 20, 1939. In May and June of 1939 he suffered several episodes of pain in the anterior part of the chest, radiating to the axillas. In October 1939 he noticed increasing dyspnea on exertion. At this time it was observed that his voice became high pitched and hoarse. Four weeks before admission he developed a dry, high-pitched cough, which persisted.

On admission, the physical examination revealed the following: The heart did not appear enlarged; the heart sounds were of poor quality but regular. The blood pressure was 102 systolic and 76 diastolic. Examination of the larynx showed a left recurrent laryngeal paralysis. The laboratory examination did not reveal anything significant. A six foot film of the heart showed the heart moderately increased in transverse diameter. An electrocardiogram showed low voltage with depressed T in all leads. The spinal fluid was negative; the venous pressure was 6 cm. of water. Circulation time studies were as follows: ether time 7 seconds, decholin circulation time 27 seconds.

The patient was discharged on December 30 with a diagnosis of myocardial deficiency, probably secondary to coronary disease.

He was readmitted on April 20, 1940. There had been increasing dyspnea on exertion since the discharge from the hospital. At this time there was definite evidence of increase in heart size, and signs of increasing congestive failure. The abdomen showed some distention and there was definite enlargement of the liver. On May 5, 1940, studies of circulation time showed the following: ether time 25 seconds, decholin circulation time 35 seconds. The venous pressure was 20 cm. of water. At this time a diagnosis of pericardial effusion was suspected, and on May 11, 1940, a pericardial puncture was done and 450 cc. of yellow fluid removed. This was followed by some improvement.

On July 16 another pericardial puncture was carried out and 600 cc. of thin, bloody fluid was removed and 400 cc. of air injected. On July 18, a chest film showed a typical hydro-pneumopericardium. On July 29 sodium sulfapyridine 3 Gm. dissolved in 30 cc. of distilled water was injected intravenously. One hour later a pericardial puncture was carried out; 600 cc. of bloody fluid was removed and 300 cc. of air injected. Estimation was made for free sulfapyridine in both the blood and the pericardial fluid at one hour and also at ninety minutes after administration of the drug. The results are summarized in the accompanying table. The pericardial fluid contained 4 Gm. of protein per hundred cubic centimeters.

A chest film taken two days later again showed the characteristic picture of a hydro-pneumopericardium. A loud friction rub could be heard following pericardial puncture. The patient developed increasing heart failure and died on Aug. 15, 1940.

An autopsy was done by Dr. L. J. Tragerman, and the anatomic diagnoses were:

1. Pericarditis, subacute, with effusion, etiology undetermined.
2. Pulmonary thrombosis.
3. Pulmonary atherosclerosis.
4. Chronic passive hyperemia of parenchymatous organs.

CASE 2.—J. H., a boy aged 17 years, admitted to the hospital on July 18, 1940, had entered the hospital on many occasions since 1938. He had suffered from bronchial asthma since 2½ years of age. During his first admission a muscle biopsy revealed the characteristic lesion of periarteritis nodosa. He also developed a pericardial effusion while in the hospital, and a paracentesis revealed fluid containing cells all of which were eosinophils. Since 1938 there had been repeated hospital admissions for severe status asthmaticus, but on three occasions he had entered the hospital with signs of cardiac decompensation and evidence of a pericardial effusion. On his last admission

he showed definite dyspnea and orthopnea, distention of the jugular veins (venous pressure 22 cm. of water) enlargement of the liver and edema of the ankles. There was a rapid increase in the cardiac dulness and heart size by roentgen examination. Paracentesis of the pericardium was indicated, and sulfathiazole was administered in order to study the diffusibility of the drug into the pericardium. The drug was given in the following dosage: on August 16, 2 Gm. in divided doses; on August 17, 3 Gm.; on August 18 and 19, 4 Gm.; on August 20, 6 Gm., and on the morning of August 21, 3 Gm. was administered in one dose.

The blood level for sulfathiazole at 10:30 a. m. August 21 was 4.8 mg. At 11:30 a. m. 550 cc. of turbid pericardial fluid was removed and 250 cc. of air injected. The sulfathiazole level of the pericardial fluid was 4.7 mg. The specific gravity of the pericardial fluid was 1.011, the protein content 3 Gm. per hundred cubic centimeters.

After approximately a week there was evidence of reaccumulation of fluid in the pericardium, and the patient was prepared for another pericardial paracentesis. On August 29 he received 1.5 Gm. of sulfanilamide, and on August 31 and September 1 received 3 Gm. daily of the drug. On September 2 the blood sulfanilamide level was 4.0 mg. At this time 400 cc. of pericardial fluid was removed. The sulfanilamide level of the pericardial fluid was 4 mg.

*Blood and Pericardial Fluid Levels of Sulfonamide Compounds in Milligrams of Free Compound per Hundred Cubic Centimeters*

Patient	Compound	Blood Level	Pericardial Fluid Level
H. O. ....	Sulfapyridine, sodium salt 3 Gm. by vein	6 mg., 60 minutes after injection 6 mg., 90 minutes after injection	1.9 mg., 60 minutes after injection 2.3 mg., 90 minutes after injection
J. H. ....	Sulfathiazole 22 Gm. by mouth in 5 days	4.8 mg.	4.7 mg.
J. H. ....	Sulfanilamide 10.5 Gm. by mouth in 4 days	4.0 mg.	4.0 mg.

A comparative study was also made of the blood protein and the pericardial fluid protein. The total blood protein was 7.3 Gm., the pericardial fluid protein 1.3 Gm. per hundred cubic centimeters.

## COMMENT

These observations indicate that there is a free diffusion of sulfanilamide and sulfathiazole into the pericardial sac. A possible explanation for the lower levels of sulfapyridine in the pericardial fluid is that a sufficient time had not elapsed for a more complete removal of the drug from the blood. This, however, seems unlikely, as the observations of Marshall and Long<sup>7</sup> indicate that after an intravenous injection of sodium sulfapyridine the distribution of the drug between the blood and the body tissues is complete or nearly complete from five to ten minutes after the injection is completed.

The practical implication of these observations is quite obvious. It is important in administering these drugs to be certain that they reach the affected tissues in concentrations which have a therapeutic effect.

Since infection of the pericardium may be due to organisms such as the pneumococcus, streptococcus and staphylococcus, which are susceptible to the sulfonamide compounds, these drugs should be indicated in pericardial inflammations due to these organisms.

658 South Bonnie Brae Street.

7. Marshall, E. K., Jr., and Long, P. H.: The Intravenous Use of Sodium Sulfapyridine, *J. A. M. A.* 112:1671 (April 29) 1939.

STUDIES ON THE PHARMACOLOGY  
OF SULFAPYRIDINE AND  
SULFATHIAZOLETHE ABSORPTION OF THE FREE ACID, THE  
SODIUM SALT AND THE GLUCOSIDE  
FROM THE ALIMENTARY TRACT

O. W. BARLOW, M.D., PH.D.

AND

D. R. CLIMENKO, M.D., PH.D.

RENSSELAER, N. Y.

It is well known that the absorption of certain sulfanilamide derivatives, such as sulfapyridine and sulfanilyl-sulfanilamide, from the gastrointestinal tract is extremely erratic, so that marked variations in blood concentrations occur in different individuals after unit dosages. Some time ago Marshall and his co-workers<sup>1</sup> took issue with the oral L. D.<sub>50</sub> for sulfapyridine in mice as reported by Wien.<sup>2</sup> They contended that the latter author used the water insoluble free acid for determining toxicity levels, which is absorbed in so irregular a manner as to render the results unreliable. Marshall showed that when the sodium salt was administered instead of the free acid a definite relationship could be demonstrated between the dosage and the blood level; the L. D.<sub>50</sub> of sulfapyridine administered as the water soluble sodium salt was approximately one-eighth that of the free acid as obtained by Wien.

The freely soluble sulfapyridine sodium is rapidly converted to the insoluble free acid when placed in an acid medium or when the high alkalinity of the solution is materially reduced. It would be reasonable to expect, therefore, that in the stomach of an individual with a normal or high hydrochloric acid level the sodium salt would rapidly be converted to the free acid. Any

intestinal tract should therefore be primarily a function of the quantity of free acid in the stomach and the emptying time of the stomach.

Our experiences in determining the oral toxicity of sulfathiazole and certain related compounds have closely paralleled those of Marshall with sulfapyridine in that we found it impossible to obtain clear cut, reproducible values after the oral administration of the insoluble free acids, whereas such results were obtainable after the oral administration of the sodium salts. These data have already been presented.<sup>3</sup>

It is believed that the differences in rate of absorption of the various forms of these chemotherapeutic agents which we observed was of sufficient practical importance to warrant careful examination. In a series of experiments both the sodium salts and the free acids of the drugs in question were administered to the same experimental individuals and their absorption and excretion were determined by the concentration of the drug in the blood, urine and feces. In addition, certain of our experimental groups were also used for a similar study on the glucose derivatives of these compounds, and on the effect of the simultaneous administration of antacids.

The first series consisted of a group of nine normal adult monkeys (*Macacus rhesus*) of both sexes. The animals were kept on a normal mixed diet, and in all instances the drugs were administered by stomach tube prior to the morning meal, a uniform dose of 1 Gm. per kilogram of the compounds being used throughout the series. In the case of the free acids of sulfapyridine and sulfathiazole, a very finely ground 100 mesh powder was suspended in a sufficient quantity of milk to make 10 per cent suspensions. A high speed rotary blender was used to make uniform suspensions. The sodium salts were administered as 10 per cent aqueous solutions. Blood concentrations were determined by means of a slight modification of Marshall's method. The results given in chart 1 were obtained. The mean values, noted in milligrams per hundred cubic centimeters, are shown diagrammatically. A study of these results brings out the following points:

1. The aqueous solutions of the sodium salts of sulfathiazole and sulfapyridine are absorbed from the gastrointestinal tract

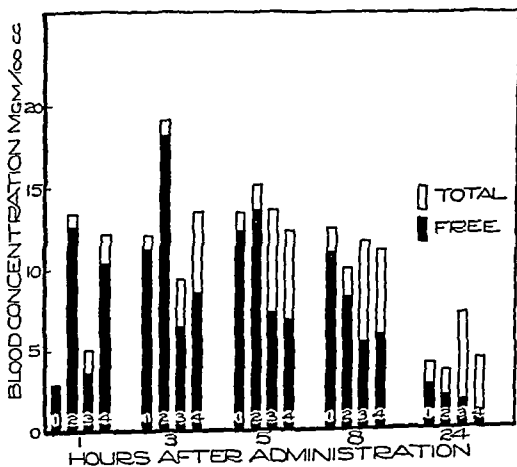


Chart 1.—Blood concentrations in monkeys (*Macacus rhesus*) following the oral administration of 2-Sulfanilamidopyridine and its soluble sodium salt, 2, sulfathiazole (so) (sodium salt).

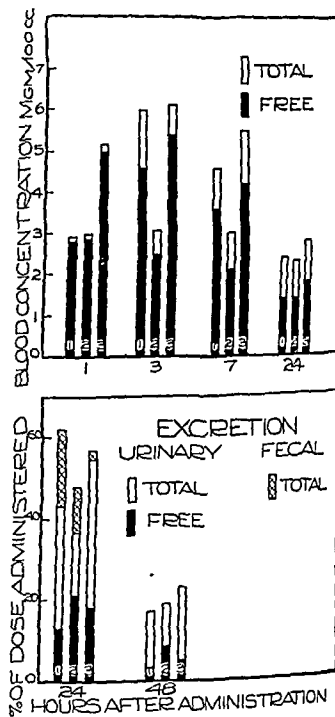


Chart 2.—Blood, urine and fecal concentrations of sulfapyridine following the oral administration of a single dose (4 Gm.) as the free acid, the sodium salt and the glucoside, to men. Form of administration: 1, acid. 2, glucoside. 3, sodium salt.

material which would pass unchanged out of the stomach into the small intestine would be absorbed as the sodium salt. The absorption of such a salt from the gastro-

From the Research Laboratories of the Winthrop Chemical Company, Inc.

1. Marshall, E. K., Jr.; Bratton, A. C., and Litchfield, J. R., Jr.: The Toxicity and Absorption of 2-Sulfanilamidopyridine and Its Soluble Sodium Salt, *Science* 88: 597, 1938.

2. Wien, R.: The Toxicity of 2-Sulfanilamidopyridine, *Quart. J. Pharm. & Pharmacol.* 11: 217, 1938.

3. Report on the Pharmacology and Toxicology of Sulfathiazole Submitted to the Bureau of Food and Drugs, U. S. Department of Agriculture, by the Winthrop Chemical Company.



more rapidly than are the suspensions of their respective free acids.

2. The sodium salt of sulfapyridine behaves in the same manner as does the sodium salt of sulfathiazole.

3. The peak concentration following the administration of a given dose of the sodium salt of either compound is considerably higher than the peak concentration after the same quantity of the free acid. The differences are maximal at the expiration of one hour and are demonstrable in decreasing degree up to the seventh hour but largely or completely disappear thereafter.

4. In the case of the monkey (*Macacus rhesus*), a much larger proportion of sulfapyridine is conjugated than of sulfathiazole. This is true regardless of whether the drug is administered as the free acid or the sodium salt.

Because of the two anomalous results which were observed in this series, the detailed protocol of the experiment is given in table 1.

the sodium salt or the glucoside was administered, for example, the dose was adjusted to contain 4 Gm. of the free acid. In some instances, sulfathiazole was administered as the free acid in capsule form followed immediately by aqueous suspensions of sodium bicarbonate or magnesium oxide.

The results of this experiment are shown in detail in table 2, while charts 2 and 3 give the mean values obtained.

With doses of this order the absorption of sulfapyridine is somewhat greater than the absorption of sulfathiazole. The blood concentrations of the free or uncombined (and therapeutically effective) form of the two drugs are the same for the two compounds. The total blood concentration of sulfapyridine, however, is considerably higher than the total blood concentration of sulfathiazole because of the fact that the degree of

TABLE 1.—Blood Concentrations in Milligrams per Hundred Cubic Centimeters in a Series of Monkeys Following the Oral Administration of Sulfapyridine and Sulfathiazole as the Free and the Sodium Salt

Monkey No.	Blood Concentration, Mg. per 100 Cc.									
	1 Hour		3 Hours		5 Hours		8 Hours		24 Hours	
	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total
28	3.9	3.9	16.0	17.6	12.8	13.7	12.5	14.6	1.2	1.6
	...	...	7.3	10.9	6.7	14.4	3.7	8.8	2.9	8.9
	21.0	21.9	33.6	35.2	23.2	25.2	13.8	15.0	0.9	1.3
	12.7	15.6	8.4	15.2	5.6	13.7	4.3	10.9	0.6	1.3
29	1.0	1.0	12.2	12.0	13.9	15.6	15.0	16.7	2.7	3.5
	1.3	1.9	4.6	6.0	6.0	11.7	4.6	10.7	1.1	8.5
	13.9	14.5	14.0	16.3	11.9	12.5	5.1	5.7	0.6	0.7
	8.9	10.8	6.7	13.3	4.7	11.9	3.5	10.6	0.7	2.1
30	3.1	3.1	11.7	13.7	13.0	14.9	9.3	10.7	1.1	1.1
	5.9	7.6	7.7	11.5	7.1	14.4	4.3	10.6	0.8	4.8
	11.2	11.6	21.2	22.2	14.1	14.7	6.5	7.6	0.9	1.2
	7.4	10.1	4.7	10.5	3.4	9.5	2.3	8.2	0.5	1.7
31	2.6	3.0	11.1	12.6	13.8	15.6	8.2	10.7	5.1	15.3
	3.2	6.2	4.3	9.2	7.4	20.1	6.8	22.8	...	...
	13.4	17.0	13.2	14.0	17.3	25.5	12.4	24.0	6.8	19.4
	...	...	...	...	...	...	...	...	...	...
32	2.8	2.8	8.9	9.2	9.7	9.7	12.5	13.2	1.2	1.6
	2.5	3.1	6.8	8.8	9.6	13.5	8.7	12.5	1.4	8.7
	17.5	17.8	19.8	21.6	15.9	16.4	5.7	6.3	2.4	2.4
	15.9	17.3	14.7	22.7	11.9	18.3	10.9	17.5	2.3	12.8
33	4.8	4.8	12.5	13.3	16.3	17.7	9.7	11.1	1.3	1.7
	3.7	5.4	4.5	7.3	3.8	9.7	3.2	7.8	1.0	1.2
	6.6	6.6	3.4	4.0	3.8	4.2	2.8	2.8	0.8	1.0
	8.0	10.5	4.3	9.0	2.9	7.8	1.6	4.7	0.5	0.9
34	3.8	3.8	10.3	10.3	12.5	13.0	8.2	9.0	5.3	6.4
	3.4	3.7	5.6	6.5	5.6	8.3	5.7	9.5	2.3	7.9
	10.0	10.0	20.4	20.4	13.0	13.0	7.9	8.8	3.2	3.4
	15.7	16.6	9.9	13.2	9.1	13.3	8.3	12.7	1.0	3.5
35	2.4	2.4	12.2	12.9	11.8	12.4	13.2	14.7	1.7	1.7
	5.4	6.6	10.3	13.3	10.0	15.4	5.9	10.3	1.7	4.9
	3.2	3.8	16.3	16.5	9.9	9.9	5.5	5.8	1.2	1.6
	11.1	12.4	15.7	20.5	12.9	18.3	10.3	15.2	0.9	2.0
36	1.2	1.2	6.3	7.0	7.6	8.5	10.4	12.0	3.6	3.7
	3.5	4.4	7.3	10.3	8.9	15.3	5.7	11.9	1.7	12.0
	16.5	17.1	21.7	22.9	14.9	15.8	13.5	14.2	1.1	1.2
	2.5	3.8	3.7	6.9	4.4	6.5	4.8	8.8	1.5	9.6

Monkey 33 showed a generally lower blood level after the administration of the sodium salt of sulfathiazole than after the administration of the same quantity of the free acid. This reversal was evident also following the administration of sulfapyridine and its sodium salt. Monkey 36 absorbed sulfathiazole and its sodium salt in the normal manner; i. e., the blood level was considerably higher after the administration of the sodium salt than after the administration of the free acid. However, this relationship was reversed when sulfapyridine and its sodium salt were administered, for the administration of the free acid gave rise to a generally higher blood concentration than was observed after the administration of the sodium salt. These anomalies will be discussed later.

A similar experiment was carried out on a group of six normal men. A fixed dose of 4 Gm. of the drug was administered to all individuals regardless of the form of the drug or the size of the subject. When

conjugation of sulfapyridine is much greater than that of sulfathiazole.

This difference in the degree and rate of conjugation of the two compounds also manifests itself in the urinary excretion of the two drugs. Approximately 40 per cent of the total amount of each drug administered is excreted in the urine in the first twenty-four hours; in the case of sulfapyridine 30 per cent of the drug excreted is in the free form, while the remainder has been acetylated; in the case of sulfathiazole 77 per cent of the excreted drug is in the free form. The relative degree of conjugation which occurs in animals and in man is the same regardless of whether the drug is administered in the form of the free acid or of the soluble sodium salt.

The absorption of either sulfapyridine or sulfathiazole from the gastrointestinal tract is more rapid, and a persistently higher blood level is maintained throughout the entire period of observation after the administration of

the sodium salt as compared with the poorly soluble free acids. Another point observed in the monkey series is also shown here. The total blood concentration after the administration of the sodium salt of sulfapyridine is somewhat higher than that which is observed following the administration of the sodium salt of sulfathiazole. This difference is due entirely to the greater proportion of conjugated sulfapyridine present: the concentrations of the free form of the drugs are the same.

In addition to the higher blood concentrations following the administration of the drugs as the sodium salts, the increased absorption rate manifests itself by an

data. A barium sulfate test meal<sup>4</sup> was administered by stomach tube, and the animals were examined under the fluoroscope at periodic intervals thereafter. Two animals in the series had a marked increase in the emptying time of the stomach associated with spasm of the pylorus. These animals also showed the anomalous result in the absorption of the free acids and the sodium salts. It would be reasonable to assume that a similar mechanism was involved in the reversal of the absorption rate seen in subject E. O., who likewise showed a retention and complained of persistent nausea, regurgitation of gastric contents and heartburn after the administration of the sodium salt.

TABLE 2.—Blood Concentrations in Milligrams per Hundred Cubic Centimeters; Urinary and Fecal Excretions as Percentage of Dose Administered in Man Following Oral Administration of 4 Gm.

Subject	Drug	Blood Concentration, Mg. per 100 Cc.										Urinary Excretion as Percentage of Dose Administered				Fecal Excretion as Percentage of Dose Administered				Notes
		1 Hour		3 Hours		7 Hours		24 Hours		48 Hours		24 Hours		48 Hours		24 Hrs.		48 Hrs.		
		Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	
E. O.		3.3	4.0	4.7	6.2	3.4	5.2	1.2	2.4	...	...	17.0	62.0	2.5	13.0	15.5	...	...	...	Nil
		3.3	3.3	4.8	5.3	3.6	4.6	1.4	2.2	Trace	...	18.0	61.0	3.5	19.0	5.0	3.5	...	...	Nausea; dizzy
		2.1	2.1	2.1	2.9	1.9	3.0	0.9	1.8	...	...	14.0	45.0	3.5	19.0	12.0	...	...	...	Nil
	bonate.....	3.9	3.9	6.7	6.7	3.3	3.7	1.0	1.0	...	...	58.0	78.0	4.5	8.0	...	...	...	...	Nil
J. O'C.	Sulfapyridine.....	2.2	2.4	5.0	5.7	4.7	5.7	1.2	2.1	...	...	11.0	35.0	3.2	15.0	17.5	...	...	...	Nil
	Sodium sulfapyridine.....	6.1	6.2	6.5	7.6	4.8	7.0	1.7	3.2	0.0	0.4	16.7	53.5	5.0	24.5	0.6	1.3	...	...	"Upset stomach"; no nausea
	Sulfapyridine glucoside.....	2.7	2.8	1.8	2.3	2.2	3.2	2.2	3.9	1.5	3.1	11.0	32.7	8.0	35.5	5.5	...	...	...	Nil
	Sulfathiazole plus sodium bicarbonate.....	3.7	3.7	3.8	4.1	2.1	2.3	1.3	1.3	...	...	27.2	36.7	5.2	8.0	...	...	...	...	Nil
H. K.	Sulfapyridine.....	2.4	2.4	4.1	5.0	2.7	3.4	1.9	2.6	...	...	10.5	34.0	5.5	22.7	25.7	...	...	...	Nil
	Sodium sulfapyridine.....	5.6	6.2	5.0	5.4	4.2	4.9	2.0	2.9	0.0	0.3	19.2	54.2	6.0	27.5	1.3	1.8	...	...	Slight nausea; dizzy
	Sulfapyridine glucoside.....	3.8	4.0	3.5	4.0	2.3	2.7	0.9	1.2	...	...	33.7	44.7	13.7	20.0	13.0	...	...	...	Nil
	Sulfathiazole plus sodium bicarbonate.....	4.2	4.2	9.0	9.5	3.6	3.6	1.2	1.2	...	...	58.5	75.5	5.5	8.2	...	...	...	...	"Blood to head"
M. F.		2.4	2.4	4.0	4.4	3.8	4.2	1.0	1.1	...	...	24.7	37.2	3.2	5.2	11.5	...	...	...	Nil
		7.3	7.3	5.8	5.8	3.3	3.4	0.9	0.9	...	...	44.7	60.5	2.7	7.0	6.7	0.5	...	...	Nausea; "gas"
		3.6	3.6	3.4	3.5	2.3	2.5	1.1	1.1	...	...	33.0	47.5	6.0	9.7	12.5	...	...	...	Nil
W. K.	nesium	6.7	6.7	7.4	7.5	4.8	4.8	1.8	1.8	...	...	18.5	24.5	6.5	9.2	...	...	...	...	Diarrhea; dizzy
	oxide.....	1.3	1.3	4.6	4.6	4.5	4.6	1.1	1.3	...	...	44.5	55.2	7.7	11.0	0.2	...	...	...	Slight cyanosis
D. S.		4.6	4.6	6.9	6.9	4.7	5.2	1.2	1.2	0.0	0.0	60.2	72.0	6.2	9.2	0.5	...	...	...	Dizzy
		2.5	2.5	4.0	4.1	3.5	3.7	3.9	4.5	3.7	...	24.2	35.7	16.2	29.5	0.1	1.1	...	...	Nil
	nesium	0.5	0.5	7.6	7.6	5.5	5.5	1.8	2.1	...	...	75.7	90.5	7.5	10.0	...	...	...	...	Diarrhea
	oxide.....	2.1	2.1	4.4	4.5	2.3	2.4	0.6	0.8	...	...	20.7	26.0	5.7	8.0	Trace	...	...	...	Sluggish
E. M.		4.7	4.7	7.3	7.3	3.8	4.0	0.9	0.9	0.0	...	55.0	70.7	4.7	6.5	1.5	2.2	...	...	Nausea; "gas"
		4.1	4.1	3.7	3.7	2.3	2.3	1.3	1.3	...	...	36.7	44.5	11.7	15.5	20.5	...	...	...	Nil
	oxide.....	3.0	3.0	5.8	5.8	4.3	4.3	1.2	1.2	...	...	26.1	32.2	8.7	11.7	...	...	...	...	Diarrhea

increase in the urinary output of the drugs. Here again the difference in the rate of conjugation of the pyridine derivative and the thiazole derivative is obvious. In the human series one anomalous result was observed similar to that recorded in the series of monkeys: Subject E. O. showed a higher blood level following the administration of sulfapyridine as the free acid than he did after the administration of the same dose of the drug in the form of the sodium salt. As we mentioned before, the absorption of such a salt from the gastrointestinal tract is a function of the rapidity with which the drug leaves the stomach and the amount of acid in the stomach. An attempt was made to correlate the degree of gastric acidity with the absorption of the sodium salts in the series of monkeys. On three occasions the response of the fasting animals to the subcutaneous injections of histamine was examined. The results, however, were so variable as to afford little help in elucidating the problem. This variation was undoubtedly due to the excitement associated with restraining the animals and passing the stomach tube. The emptying time of the stomach, however, gave better

The water soluble glucosides of these compounds, while susceptible to hydrolytic breakdown, are more stable to  $p_H$  change than their respective sodium salts. We have observed the precipitation of the free acid at the point of contact during the injection by syringe of a 5 per cent solution of sodium sulfapyridine into a buffered Ringer-Locke solution at  $p_H$  7.4. When the glucoside

TABLE 3.—Uncombined Sulfapyridine and Sulfathiazole

Time of Incubation	Percentage of Drug in Uncombined Form	
	Sulfathiazole	Sulfapyridine
0 minutes.....	17.5	15.0
30 minutes.....	53.9	50.5
60 minutes.....	66.1	70.5
120 minutes.....	68.6	71.2
240 minutes.....	68.6	71.0

is incubated for one hour at 37 C. in 0.3 per cent hydrochloric acid solution, only about 50 per cent of the drug will be reduced to the uncombined form. Thus, in a

4. Bananas 400 Gm., milk 300 Gm., barium sulfate 200 Gm. and sodium bicarbonate 100 Gm.

simple experiment 10 cc. of a 10 per cent solution of the sulfapyridine glucoside was added to 50 cc. of 0.3 per cent hydrochloric acid solution and incubated at 37 C. Samples were removed at periodic intervals and analyzed for uncombined sulfapyridine. A similar system was set up with sulfathiazole glucoside.

In spite of apparently greater stability of the more soluble glucoside in the presence of acid, this compound is absorbed from the intestine considerably slower than the sodium salt and even slightly slower than the free acid. These results confirm the work of Finland, Taylor and their associates,<sup>5</sup> who were unable to show any significant difference in the absorption of sulfapyridine whether administered as the glucoside or the free acid.

Sodium bicarbonate is frequently administered in combination with sulfanilamide in order to improve the tolerance and to correct a tendency to acidosis. Acidosis rarely occurs after sulfapyridine or sulfathiazole therapy, and the absence of change in the alkali reserve

of absorption of the free acid, giving rise to a blood concentration approaching that resulting from the administration of the sodium salt. The addition of sodium bicarbonate gave rise to practically no untoward symptoms, but the addition of magnesium oxide caused diarrhea in every instance.

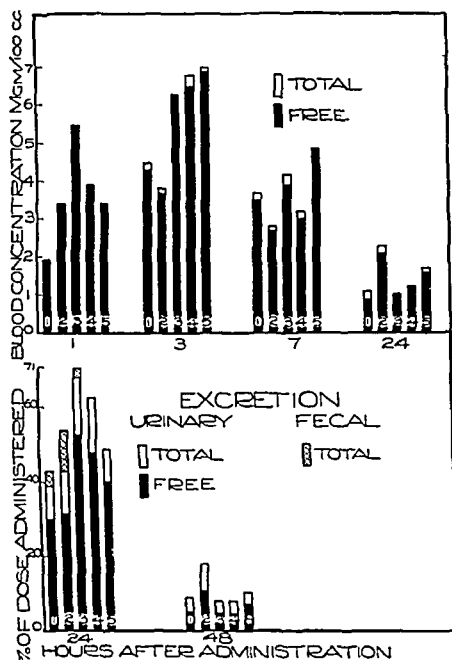


Chart 3.—Blood, urine and fecal concentrations of sulfathiazole following the oral administration of a single dose (4 Gm.) as the free acid, the sodium salt, the glucoside, the free acid in combination with sodium bicarbonate and the free acid in combination with sodium salt. Form of administration: 1, acid; 2, acid + sodium bicarbonate; 3, acid + sodium salt; 4, acid + sodium bicarbonate; 5, acid + sodium salt.

after such medication suggests that supplementary medication with antacids is unnecessary. The alteration of the usual absorption curve of sulfanilamide derivatives when administered as the sodium salts suggested that the difference noted might be due in part to an altered emptying time and seemed worthy of examination, since such alterations may be induced by the administration of antacids. Sulfathiazole was administered as the free acid in capsules followed immediately by an aqueous suspension of sodium bicarbonate or magnesium oxide in doses of 4 Gm. and 3 Gm. respectively. The addition of the alkali caused a marked increase in the rate

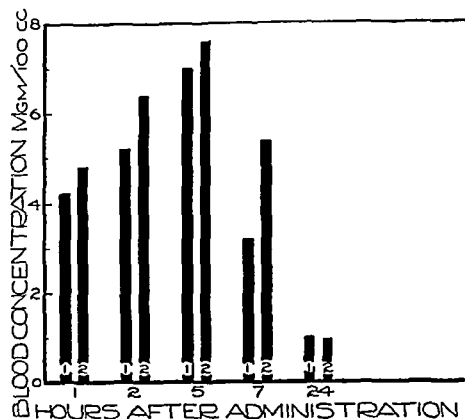


Chart 4.—Blood concentration of sulfathiazole in dogs following the oral administration of 148 mg. per kilogram of sulfathiazole as the free acid and as the glucoside: 1, sulfathiazole glucoside; 2, sulfathiazole acid.

In dogs and rats the administration of sulfathiazole in the form of the free acid and the glucoside gives essentially the same result as has been described for man. In both of these species the blood level following the administration of the glucoside more closely approaches that following the administration of the free acid than it does in man. These results are shown in charts 4 and 5.

#### SUMMARY

1. The sodium salts of sulfapyridine and sulfathiazole are absorbed from the gastrointestinal tracts of man and monkey more rapidly than are their respective free acids.
2. The glucosides of sulfapyridine and sulfathiazole are absorbed from the gastrointestinal tract of man,

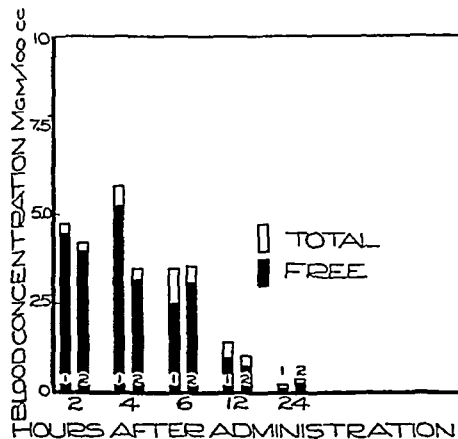


Chart 5.—Blood concentration of sulfathiazole in man following the oral administration of a single dose (250 mg. per kg.) as the free acid and as the glucoside: 1, sulfathiazole (glucoside); 2, sulfathiazole (free acid).

dogs and rats less rapidly than are their respective free acids.

3. The simultaneous administration of alkali in the form of sodium bicarbonate or magnesium oxide with sulfathiazole hastens the absorption of this compound from the gastrointestinal tract of man.

5. Taylor, F. H. L.; Lowell, F. C.; Adams, M. A.; Spring, W. C., and Finland, Maxwell: A Comparative Study of the Blood Concentration and Urinary Excretion of Sulfapyridine and Sulfanilamide After Single Doses of Sulfapyridine and Related Compounds Administered by Various Routes. *J. Clin. Investigation* 19: 201, 1940. Finland, Maxwell; Lowell, R. C.; Spring, W. C., and Taylor, F. H. L.: Intravenous Use of Sodium Sulfapyridine and Report of Clinical and Laboratory Observations on the Use of Glucose Sulfapyridine Solution. *Ann. Int. Med.* 13: 1105, 1940.

4. In rate and degree, conjugation of sulfapyridine is higher than that of sulfathiazole in man and monkey.

5. Following the oral administration of equal doses, the blood concentration of unconjugated sulfapyridine is practically the same as that of unconjugated sulfathiazole. The total blood concentration of sulfapyridine, however, is higher than the total blood concentration of sulfathiazole.

Since the completion of this work a study on the absorption and excretion of the sodium salt of sulfapyridine in man has been published by Ratish, Davidson and Bullova.<sup>6</sup> Our results support the observations made by these authors save for their conclusion that there is less acetylation following the administration of sodium sulfapyridine than after the administration of the same quantity of the drug as the free acid. The ratio of unconjugated drug to total drug is greater in the first few hours following the administration of the sodium salt than it is after the administration of the same dose of the free acid, but within seven hours after such dosage the ratio of unconjugated to conjugated drug is of the same order, regardless of the form in which it was administered.

33 Riverside Avenue.

## THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS

### PRESENT STATUS

S. S. LICHTMAN, M.D.

AND

WILLIAM BIERMAN, M.D.

NEW YORK

Until recently all forms of treatment of patients with subacute bacterial endocarditis were adjudged ineffective. Except for a rare spontaneous remission of the disease, the outcome has generally been accepted as fatal. The recent application of artificial hyperthermia and new chemotherapeutic agents to the treatment of bacterial infections fostered the hope that the outlook for recovery in subacute bacterial endocarditis might improve.

In 1933 one of us (W. B.) applied physically induced pyrexia without additional chemotherapy to a patient suffering from subacute bacterial endocarditis. At the time this patient was actively embolizing. Following the second fever treatment showers of numerous emboli caused an exitus. Postmortem examination showed the viscera to be filled with numerous fresh and old emboli.

In 1936 Krusen<sup>1</sup> experimented with artificial fever therapy in subacute bacterial endocarditis and abandoned it because of apparently increased danger of embolism. In 1937 Dry and Willius<sup>2</sup> treated 4 patients who had proved subacute bacterial endocarditis with therapeutic fever and concluded that, despite the fact that fever therapy enhanced cellular reactions and the defense processes of the host, *Streptococcus viridans* appeared to be able to resist the highest temperature

to which it is safe to expose the human body. The results with gonococcal endocarditis were far more encouraging; however, the results of treatment of this form of endocarditis will not be included in this communication.

In 1938 Baehr and Bierman<sup>3</sup> successfully treated a patient with hyperpyrexia and sulfanilamide. Clubbing of the fingers disappeared within three weeks after the blood culture became sterile. In 1940 Krusen and Bennett<sup>4</sup> treated six patients with combined fever and sulfanilamide without success. The combined therapy appeared to have a definite although transient influence on the disease; either a definite decrease occurred in the number of bacterial colonies on culture of the blood following treatment, or the blood cultures became negative temporarily. Encouraged by White's<sup>5</sup> observation that the bactericidal properties of sulfanilamide were increased one hundredfold with a rise of temperature from 37 to 39 C., Solomon<sup>6</sup> proceeded to treat patients who had subacute bacterial endocarditis with artificial hyperpyrexia induced by the intravenous use of killed typhoid-paratyphoid bacilli.

### MATERIAL

The number of cases treated by the new methods is now large enough to permit a preliminary estimate of the value of the respective forms of treatment. Published reports and our own experience have been reviewed in an effort to arrive at a tentative conclusion as to which method of treatment at present offers the greatest hope for recovery from the disease. For this purpose only permanent cures are significant.

The presentation consists of 55 patients with subacute bacterial endocarditis due to *Streptococcus viridans* or nonhaemolyticus<sup>7</sup> treated at the Mount Sinai Hospital between the period of January 1939 and September 1940 and 232 cases collected from other sources (total, 287 cases). Only cases that received adequate treatment were selected. There were four complete recoveries in our series and twenty-one in the entire group. The material is presented under the following headings:

Spontaneous remission reported in the literature.

Recovery from the use of sulfonamide drugs.

Recovery from use of "combined methods," i. e. the combination of sulfonamide therapy and other measures (i. e. heparin; physical hyperthermia; intravenous typhoid-paratyphoid; radiotherapy).

*Spontaneous Remissions.*—Spontaneous recoveries from subacute bacterial endocarditis due to *Streptococcus viridans* or nonhaemolyticus are reported by Horder,<sup>8</sup> Murray,<sup>9</sup> Capps,<sup>10</sup> Libman,<sup>11</sup> Bögenderfer,<sup>12</sup>

3. Bierman, William, and Baehr, George: The Use of Physically Induced Pyrexia and Chemotherapy in the Treatment of Subacute Bacterial Endocarditis, this issue, p. 292.

4. Krusen, F. H., and Bennett, R. L.: Unsuccessful Treatment of Subacute Bacterial Endocarditis with Combined Fever and Sulfanilamide Therapy, Proc. Staff Meet., Mayo Clin. 15: 328 (May 22) 1940.

5. White, H. J.: The Relationship Between Temperature and the Streptococcal Activity of Sulfanilamide and Sulfapyridine in Vitro, J. Bact. 38: 549 (Nov.) 1939.

6. Solomon, H. A.: Subacute Bacterial Endocarditis: Treatment with Sulfapyridine and Intravenous Injections of Typhoparatyphoid Vaccine, New York State M. J. 41: 45 (Jan.) 1941; personal communication to the authors.

7. A single case of *Bacillus influenzae* (*Haemophilus influenzae*) endocarditis was included.

8. Horder, T.: Infective Endocarditis, Quart. J. Med. 2: 289, 1903-1909.

9. Murray, L. M.: Subacute Bacterial Endocarditis, Ann. Clin. Med. 1: 18, 1922.

10. Capps, J. A.: The Arsenical Treatment of Chronic Infectious Endocarditis, Am. J. M. Sc. 165: 40 (Jan.) 1923.

11. Libman, Emanuel: A Consideration of the Prognosis in Subacute Bacterial Endocarditis, Am. Heart J. 1: 25 (Oct.) 1925.

12. Bögenderfer, L.: Zur Prognose der Endocarditis lenta, Deutsche Arch. f. klin. Med. 154: 60, 1927.

6. Ratish, H. D.; Davidson, A., and Bullova, J. G. M.: The Absorption and Excretion of Sulfapyridine and of Sodium Sulfapyridine in Man, J. Pharmacol. & Exper. Therap. 69: 364, 1940.

From the Medical Division, Service of Dr. George Baehr and the Department of Physical Therapy, the Mount Sinai Hospital, Material presented at the Scientific Exhibit of the Graduate Fortnight of the New York Academy of Medicine on "Infections," October 1940.

1. Krusen, F. H.: Present Status of Fever Therapy Produced by Physical Means, J. A. M. A. 107: 1215 (Oct. 10) 1936.

2. Dry, T. J., and Willius, F. A.: Fever Therapy for Subacute Bacterial Endocarditis, Proc. Staff Meet., Mayo Clin. 12: 321 (May 26) 1937.

Schottmueller,<sup>13</sup> Libman,<sup>14</sup> Kissling,<sup>15</sup> Middleton and Burke.<sup>16</sup> There are series of cases, however, in which no spontaneous recoveries have been noted (Warren and Herrick,<sup>17</sup> Thayer,<sup>18</sup> Capps,<sup>19</sup> Major<sup>20</sup>).

The most favorable outlook for spontaneous recovery from subacute bacterial endocarditis may be found in Libman's<sup>14</sup> study of his first 150 cases of the disease (of the "usual type of severity"). In this group of cases carefully studied and followed there were four complete recoveries, or 3 per cent. In a subsequent report Libman<sup>14</sup> enumerated twelve recoveries in patients "with the usual type" of the disease in a total of 1,000 cases. Three per cent probably represents the most favorable incidence of spontaneous recovery.

**Recovery from the Use of Sulfonamide Drugs.**—Isolated, successfully treated cases have been reported by McQuarrie,<sup>21</sup> Barton and Stinger,<sup>22</sup> Heyman<sup>23</sup> and Christie.<sup>24</sup> Recoveries occurring among groups of cases of subacute bacterial endocarditis treated with the sulfonamide drugs have also been reported by Major and Leger<sup>25</sup> and Major.<sup>26</sup> Long<sup>26</sup> to date has treated 117 patients with the sulfonamide drugs with seven recoveries. In our own series, 22 cases of subacute bacterial endocarditis were treated with one recovery. Isolated cases treated unsuccessfully (Barnett, Hartman, Perley and Ruhoff,<sup>27</sup> Sailer<sup>28</sup>) as well as groups of cases treated unsuccessfully have been reported (Klee and Römer,<sup>29</sup> Ellis,<sup>30</sup> Whitby,<sup>31</sup> Bliss, Long and Feinstone,<sup>32</sup> Kinell and Ernstene,<sup>33</sup> Kolmer,<sup>34</sup> Steele<sup>35</sup>).

The results of sulfonamide chemotherapy have been tabulated (table 2). In a total of 198 cases reported

in the literature and those in our series recovery occurred in 12, or 6 per cent. Four additional isolated cases of recovery have been reported, totaling 16. The percentage of recovery including the latter 4 cases cannot be stated, however, as the total number of cases treated is not known.

**Recovery from Treatment with Combined Methods, i. e. the Combination of Sulfonamide Therapy and Other Measures.**—Under this heading are included cases that have been adequately treated by chemotherapy and some additional form of therapy.

TABLE 1.—Spontaneous Recoveries in Subacute Bacterial Endocarditis

	Number of Cases	Number of Recoveries	Percentage of Recoveries
1. Libman <sup>14</sup> .....	150	4	3%
2. Horder <sup>8</sup> .....	150	1	...
3. Thayer <sup>18</sup> .....	206	0	...
4. Warren and Herrick <sup>17</sup> .....	25	0	...
5. Major <sup>20</sup> .....	15	0	...
6. Middleton and Burke <sup>16</sup> .....	88	1	...
Total.....	634	6	1%

A. Chemotherapy Combined with Heparin: There are 43 cases in this group. Kelson and White<sup>36</sup> treated 26 patients with combined sulfonamide and heparin, and 4 patients recovered. This series includes the 6 cases originally reported by these authors. Deitrick<sup>37</sup> treated 4 patients at the New York Hospital with no recoveries. Thirteen of the patients in our series were treated in this fashion with one recovery.<sup>38</sup> Of the total of 43 patients treated, 5, or 11.5 per cent, recovered (table 3). Only those patients who received physiologically active heparin adequate in dosage to produce prolongation of the blood coagulation time to over an hour were selected for this study. Kelson and White<sup>36</sup> have emphasized that heparin therapy should be instituted after chemotherapy has sterilized the blood stream.

B. Chemotherapy Combined with Hyperthermia: A total of 25 patients have been treated in this manner. Four of the entire series, 16 per cent, recovered (table 3). Six of the cases were treated unsuccessfully by Krusen and Bennett.<sup>4</sup> Ferderber<sup>40</sup> treated 3 cases with two successful results. Bierman and Baelir have observed two recoveries in a group of 16 cases treated at the Mount Sinai Hospital. One of the patients in this series who recovered had previously received six radium exposures over the precordium without clinical effect.<sup>3</sup>

Bierman stresses the necessity of "adequate" treatment. This can be defined empirically as at least eight sessions of hyperthermia in view of the fact that the 2 patients who recovered following this form of treatment received eight or more treatments. It should be noted that 1 patient who recovered suffered from *Bacillus influenzae* (*Haemophilus influenzae*) endocarditis. The hyperthermia should be induced on alter-

36. Kelson, S. R., in discussion, Conference of the Medical Services on "Results in the Treatment of Subacute Bacterial Endocarditis by Recent New Methods," Mount Sinai Hospital, New York, May 15, 1940; personal communication to the authors. Kelson and White.<sup>27</sup>

37. Deitrick, John: Personal communication to the authors, 1940.

38. Kelson supervised the treatment of this patient at the Mount Sinai Hospital. It is included in this series with the permission of Dr. Elmer Gais.

39. Kelson, S. R., and White, P. D.: A New Method of Treatment of Subacute Bacterial Endocarditis, Using Sulfapyridine and Heparin in Combination: Preliminary Report, J. A. M. A. **113**:1700 (Nov. 4) 1939.

40. Ferderber, M. B.: Personal communication to Dr. Bierman, 1940.

13. Schottmueller, H.: Endocarditis rheumatica, Endocarditis lenta und ihre Prognose, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 3, p. 1057.

14. Libman, Emanuel: A Further Report on Recovery and Recurrence in Subacute Bacterial Endocarditis, Tr. A. M. Physicians **48**:44, 1933.

15. Kissling, K.: Eine anscheinend geheilte Endocarditis lenta (Streptococcus viridans), Med. Klin. **31**:1427 (Nov. 1) 1935.

16. Middleton, W. S., and Burke, M.: Streptococcus Viridans Endocarditis Lenta: A Clinicopathologic Analysis of the Experience in the Wisconsin General Hospital, Am. J. M. Sc. **198**:301 (Sept.) 1939.

17. Warren, M., and Herrick, W. W.: Analysis of One Hundred and Thirty-Four Cases of Bacteremia, Am. J. M. Sc. **151**:556 (April) 1916.

18. Thayer, W. S., in Symposium on Endocarditis, J. A. M. A. **82**:1721 (May 24) 1924.

19. Capps, J. A.: Subacute Bacterial Endocarditis Due to Streptococcus Viridans with Special Reference to Prognosis, Ann. Int. Med. **13**:280 (Aug.) 1939; cited by Kelson and White.<sup>36</sup>

20. Major, R. H.: The Effect of Sulfanilamide Compounds on Endocarditis, Am. J. M. Sc. **199**:759 (June) 1940.

21. McQuarrie, J. A.: Report of Cases Treated with Sulfanilamide (Aug.) 1937.

22. Barton, R. L., and Stinger, D.: Subacute Bacterial Endocarditis Treated with Sulfanilamide, J. Iowa State M. Soc. **29**:402 (Aug.) 1939.

23. Heyman, Jacob: Subacute Bacterial Endocarditis Successfully Treated with Sulfanilamide: Report of Well Established Case Eighteen Months After Recovery, J. A. M. A. **114**:2373 (June 15) 1940.

24. Christie, Amos: Subacute Bacterial Endocarditis Apparently Cured with Sulfanilamide, J. A. M. A. **115**:1357 (Oct. 19) 1940.

25. Major, R. H., and Leger, L. H.: Recovery from Subacute Infectious Endocarditis Following Prontosil Therapy, J. A. M. A. **111**:1919 (Nov. 19) 1938; Recovery from Subacute Infectious Endocarditis, J. Kansas M. Soc. **40**:324 (Aug.) 1939.

26. Long, P. H.: Personal communication to the authors, 1940.

27. Barnett, H. L.; Hartman, A. F.; Perley, A. M., and Ruhoff, M. B.: Treatment of Pneumococcal Infections in Infants and Children with Sulfanilamide, J. A. M. A. **112**:518 (Feb. 11) 1939.

28. Sailer, S.: Subacute Bacterial Endocarditis Treated with Sulfanilamide Resulting in Granulocytopenia and Death, Am. J. Clin. Path. **9**:269 (May) 1939.

29. Klee, P., and Römer, H.: Prontosil bei Streptokokkenkrankungen, Deutsche med. Wchnschr. **61**:253 (Feb. 11) 1935.

30. Ellis, G. R.: Treatment of Subacute Bacterial Endocarditis with M. & B. 693, Lancet **2**:1521 (Dec. 31) 1938.

31. Whitby, L.: Chemotherapy of Bacterial Infections, Lancet **2**:1095 (Nov. 10) 1938.

32. Bliss, Eleanor A.; Long, P. H., and Feinstone, W. H.: The Differentiation of Streptococci and Its Relation to Sulfanilamide Therapy, South. M. J. **31**:303 (March) 1938.

33. Kinell, J., and Ernstene, A. C.: Subacute Bacterial Endocarditis Treated Unsuccessfully with Sulfapyridine, Cleveland Clin. Quart. **7**:83 (April) 1940.

34. Kolmer, J. A.: Progress in Chemotherapy of Bacterial and Other Diseases, with Special Reference to the Prontosils, Sulfanilamide and Sulfapyridine, Arch. Int. Med. **65**:671 (April) 1940.

35. Steele, H. H.: Effect of Sulfanilamide on Length of Life of Patients with Subacute Bacterial Endocarditis, New England J. Med. **222**:1067 (June 27) 1940.

nate days, temperatures as high as 104 and 106 F. being maintained for periods of five hours and longer. The reaction of the patient may make it necessary to modify these factors.

C. Chemotherapy Combined with Intravenous Typhoid-Paratyphoid Vaccine: Solomon<sup>6</sup> has employed chemotherapy and hyperpyrexia induced by the intra-

TABLE 2.—Results of Sulfonamide Chemotherapy in Subacute Bacterial Endocarditis

	Number of Cases	Number of Recoveries
1. Major <sup>20</sup> .....	7	3
2. Kinell and Ernste <sup>21</sup> .....	5	0
3. Spink and Crago: Arch. Int. Med. 64: 228 (Aug.) 1939.....	11	1
4. Klee and Römer <sup>20</sup> .....	4	0
5. Ellis <sup>20</sup> .....	2	0
6. Whitby <sup>21</sup> .....	3	0
7. Bliss, Long and Feinstein <sup>22</sup> .....	3	0
8. Kolmer <sup>21</sup> .....	10	0
9. Steele <sup>25</sup> .....	14	0
10. Long <sup>20</sup> .....	117	7
11. Mount Sinai.....	22	1
Total.....	198	12
Per cent recovery.....	6.0	

venous use of typhoid-paratyphoid vaccine in 17 cases with five recoveries. His technic was used in the treatment of 4 patients in our series with unsuccessful results. Of the combined total of 21 cases treated in this manner 5, or 25 per cent, recovered (table 3).

The use of intravenous typhoid-paratyphoid vaccine to increase the fever level was used by Solomon in preference to artificial hyperpyrexia because he believes

TABLE 3.—Results with Combined Methods of Treatment of Subacute Bacterial Endocarditis

	Number of Cases	Number of Recoveries	Percentage of Recoveries
Chemotherapy, heparin			
1. Kelson and White <sup>*</sup> .....	26	4	
2. New York Hospital <sup>27</sup> .....	4	0	
3. Mount Sinai.....	13	1 †	
	43	5	11.5
Chemotherapy, hyperthermia			
1. Krusen and Bennet.....	6	0	
2. Ferderber <sup>40</sup> .....	3	2	
3. Mount Sinai.....	16	2 ‡	
	25	4	16.0
Chemotherapy, intravenous typhoid			
1. Solomon, H. A., to be published....	17	5	
2. Mount Sinai.....	4	0	
	21	5	25
Chemotherapy, radiotherapy			
Mount Sinai #.....	6	1 §	16.5
Total			
Literature.....	56	11	20.0
Mount Sinai.....	33	3	9.5
	89	14	Av. 16.0

\* Includes six cases in original report.

† Case of recovery also referred to in Kelson and White series.

‡ An additional patient is now bacteria free and afebrile for a period of four months.

# All patients in this group also treated by other measures.

§ Also treated with hyperthermia; included in two recoveries noted above under this heading.

that "by combining foreign protein shock therapy with the sulfonamides the effectiveness of the drug is enhanced not only by the hyperpyrexia produced which in itself renders the drug bactericidal instead of bacteriostatic but also by the addition of many factors in the immunity, some not clearly understood, which are activated at the same time." He states that adequate treatment by this method consists of at least six sessions

of hyperpyrexia induced by graduated doses of the vaccine. These injections should be given over a period of seven to ten days. Leukopenia and latent jaundice may follow the use of intravenous injections of typhoid bacilli combined with the use of sulfonamide drugs. It is important to differentiate the leukopenia caused by the intravenous typhoid vaccine from that produced by the toxic action of the sulfonamide drugs. In the 4 cases treated in this manner in our series, chemotherapy was continued despite the neutropenia but the intravenous injections were temporarily discontinued until the leukocyte picture returned to normal.

D. Chemotherapy Combined with Radiotherapy: Six patients received radiotherapy over the precordium in addition to chemotherapy. The only patient in this group who recovered also received nine treatments with artificial hyperpyrexia. The blood cultures remained positive despite the radiotherapy. The blood cultures became negative following the hyperthermia treatments.

TABLE 4.—Summary of Results of Treatment of Subacute Bacterial Endocarditis\*

Method of Treatment	Number Treated	Number Recovered	Percentage Recovered
Chemotherapy † alone			
Mount Sinai.....	22	1	4.5
Literature.....	176	11	6.0
	6§	4§	
Total.....	198	12	6.0
Combined therapy :			
Mount Sinai.....	32	3	9.5
Literature.....	56	11	20.0
Total.....	88	14	16.0
Total cases			
Mount Sinai.....	54	4	7.5
Literature.....	232	22	9.5
	6	4	
Total.....	286	26	9.0
	6§	4§	

\* Viridans and nonhemolytic streptococcus cases (one case due to *Bacillus* [*Haemophilus*] *influenzae* with recovery included). Maximum incidence of spontaneous recovery 3 per cent (Libman).

† Sulfonamide compounds (sulfanilamide, sulfapyridine, sulfathiazole).

‡ Individual case reports (four recoveries, 2 deaths).

§ Chemotherapy combined with (1) heparin, (2) radiotherapy, (3) hyperthermia, (4) intravenous typhoid-paratyphoid (Solomon).

It is improbable that the radiotherapy contributed to the recovery. Two patients who had chemotherapy and radiotherapy and no other procedure failed to recover. Three others treated in this manner with additional artificial hyperthermia also failed to recover.

#### COMMENT

Reports of isolated examples of recovery from subacute bacterial endocarditis after one form of therapy or another do not permit a comparison of the effectiveness of the various therapeutic procedures or an evaluation of the role played by spontaneous recovery. For this reason we are including only the results observed in reported series.

The best prospect for spontaneous recovery has been 3 per cent (Libman). The incidence of recovery from subacute bacterial endocarditis due to *Streptococcus* viridans and nonhemolyticus approximates 6 per cent following treatment with the sulfonamide drugs. Chemotherapy combined with additional forms of treatment such as heparin, artificial hyperthermia and intravenous injection of typhoid-paratyphoid vaccine yields an incidence of recovery over twice as large as that obtained with the sulfonamide drugs alone (table 4). The series of cases reported is still too small to



arrive at any final conclusion as to the value of these methods of treatment of the disease. It is apparent however that in the treatment of the active phase of the disease the newer forms of treatment promise a better chance for recovery than do the methods employed heretofore.

Clinical observations support the *in vitro* observations of White<sup>5</sup> that the addition of some form of hyperthermia to chemotherapy promotes the efficacy of the latter.

The present study warrants no definite statement as to choice of sulfonamide drug in the treatment of subacute bacterial endocarditis. Greater experience has been had to date with the use of sulfanilamide and sulfapyridine than with sulfathiazole. Favorable results have definitely been obtained with the first two of these drugs in *Streptococcus viridans* endocarditis. The former drug is better tolerated. The preference at this time appears to be for sulfapyridine. If the patient develops so-called sulfapyridine fastness, intolerance or toxicity and sulfonamide medication is to be continued, it is advisable to change to sulfanilamide. Sulfathiazole is best employed from the outset in cases of endocarditis due to unusual organisms, e. g. *B. hoffmanii*.

Optimal results may be expected from adequate treatment given at the optimum time. Early diagnosis and early intensive treatment favor recovery. Leukopenia and normal temperature are factors which decrease the bacteriostatic and bactericidal effects of the drugs. Kelson and White have recommended that heparin should first be administered after chemotherapy has rendered the blood sterile. Results from the methods producing hyperthermia may be improved by their early administration within twenty-four to forty-eight hours after chemotherapy is begun. It is advisable to maintain the hyperpyrexia for at least five hours and to repeat the treatments on alternate days if tolerated. The prospect of recovery with the combined methods of treatment may be further increased if more attention is paid in the future to the factors which enhance the effects of chemotherapy.

#### SUMMARY

Among 200 cases of subacute bacterial endocarditis due to *Streptococcus viridans* and nonhaemolyticus collected from the literature and the records of the Mount Sinai Hospital, in which the sulfonamide drugs were administered, recovery occurred in 12, an incidence of 6.0 per cent recovery.

Among 43 patients treated with combined chemotherapy and heparin 5 recovered, an incidence of 11.5 per cent recovery.

Among 24 patients treated by chemotherapy and physically induced hyperthermia 4 recovered, an incidence of 16.0 per cent recovery. Of 21 patients treated by chemotherapy and hyperthermia induced by intravenous typhoid-paratyphoid vaccine 5 recovered, an increase of 25 per cent recovery.

The number of cases in the three series treated by combined methods is still too small to yield an accurate statistical estimate of the incidence of recovery in each group. This preliminary review of the results obtained thus far is encouraging. The combined methods of therapy seem to promise a greater incidence of recovery than may be anticipated in the natural course of the disease or after treatment with the sulfonamide drugs alone.

112 East Seventy-Fourth Street—471 Park Avenue.

## LEPTOSPIROSIS: A PUBLIC HEALTH HAZARD

### REPORT OF A SMALL OUTBREAK OF WEIL'S DISEASE IN BATHERS

W. PAUL HAVENS, M.D.

CARL J. BUCHER, M.D.

AND

HOBART A. REIMANN, M.D.

PHILADELPHIA

About fifty years ago Weil<sup>1</sup> discovered an acute infectious disease with jaundice and fever to which his name was later applied. In 1914 Inada and Ido<sup>2</sup> proved the etiologic agent to be a spiral shaped micro-organism which Noguchi<sup>3</sup> shortly thereafter described in detail, naming it *Leptospira icterohaemorrhagiae*.

Since the identification of this micro-organism there has gradually accumulated knowledge of other morphologically similar but serologically and immunologically different members of the same group of leptospires.<sup>4</sup> They are distributed worldwide and are usually associated with rats and dogs. Many of them classed as *Leptospira biflexa*<sup>5</sup> are not pathogenic for man. In Europe at least three distinct pathogenic varieties are recognized: (1) *Leptospira icterohaemorrhagiae* of Weil's disease, (2) *Leptospira canicola*<sup>6</sup> of an infection in dogs transmissible to man and (3) *Leptospira grippo-typhosa*<sup>7</sup> of a syndrome known in different places as "summer influenza," "harvest fever," "mud fever," "water fever" or "swamp fever." Another variant, *Leptospira hebdomadis*, discovered by Ido and Ito,<sup>8</sup> is the cause of the "seven day fever" of Japan. Although infections caused by *Leptospira grippo-typhosa* and *Leptospira hebdomadis* have not been reported in the United States, it is probable that they occur here, since *Leptospira icterohaemorrhagiae*, *Leptospira canicola*<sup>9</sup> and *Leptospira biflexa* are present. The best discussion of the subject has been published by Walch-Sorgdrager.<sup>10</sup>

Outbreaks of disease due to pathogenic leptospires constantly occur throughout the world. In 1938, for example, an epidemic of Weil's disease broke out among rice field workers in Italy,<sup>11</sup> and hundreds of cases of "field fever" were said to have occurred among har-

From the Departments of Medicine and Pathology, Jefferson Medical College and Hospital.

1. Weil, Adolph: Ueber eine eigenthümliche, mit Milztumor, Icterus und Nephritis einhergehende, acute Infectionskrankheit, *Deutsches Arch. f. klin. Med.* **39**: 209-232, 1886.

2. Inada, R.; Ido, Y.; Hoke, R.; Kaneko, R., and Ito, H.: The Etiology, Mode of Infection and Specific Therapy of Weil's Disease (*Spirochaetosis Icterohaemorrhagiae*), *J. Exper. Med.* **23**: 377-403 (March) 1916.

3. Noguchi, Hideyo: *Spirochaeta Icterohaemorrhagiae* in American Wild Rats and Its Relation to the Japanese and European Strains, *J. Exper. Med.* **25**: 755-763 (May) 1917.

4. Karakašević, Bogdan: Serologische Untersuchungen über die *Spirochaetes* Feldfiehens ("*Spirochaeta grippo-typhosa*"), *Ztschr. f. Immunitätsforsch. u. exper. Med.* **96**: 427-439 (Oct. 2) 1939.

5. Wolbach, S. B., and Binger, L.: Notes on a Filtrable *Spirochaete* from Fresh Water: *Spirochaeta Biflexa* (New Species), *J. M. Research* **30**: 23-25, 1914.

6. Klarenhek, A., and Schüffner, W. A. P.: The Appearance in Holland of *Leptospira* Strain Differing from Weil Stain, *Nederl. tijdschr. v. geneesk.* **77**: 4271-4276 (Sept. 16) 1933.

7. Tarrasoff, Serge: Note additionelle sur l'agent infectieux de la schlammeffieber ou leptospirose grippo-typhosa aquatilis, *Ann. Inst. Pasteur* **46**: 635-638 (June) 1931.

8. Ido, Y.; Ito, H., and Wani, H.: *Spirochaeta Hebdomadis*, the Causative Agent of Seven Day Fever (Nanukayami), *J. Exper. Med.* **28**: 435-447 (Oct.) 1918.

9. Meyer, K. F.; Eddie, B., and Anderson-Stewart, R.: Canine, Murine, Human Leptospirosis in California, *Proc. Soc. Exper. Biol. & Med.* **35**: 17-19 (Feb.) 1938.

10. Walch-Sorgdrager, L.: Leptospiroses, *Bull. Health Organ., League of Nations* **5**: 143-386, 1939.

11. Mino, Prospero: Ueber Leptospirosen bei den Arbeitern der Reisfelder Oberitaliens, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **96**: 466-520 (Oct. 2) 1939.

vesters in Bavaria.<sup>12</sup> In one group<sup>12a</sup> the leptospiras were identical with *L. bataviae* from Java, where the disease, as in Italy, occurs in rice harvesters. It is probable that these outbreaks resulted from contact of large numbers of field workers in late summer with water contaminated with rat urine.

Except for severity, the various leptospiroses are usually clinically indistinguishable. The form called Weil's disease caused by *Leptospira icterohaemorrhagiae* is regarded as the most severe, since about 50 per cent of cases are said to present jaundice. In contrast, jaundice was present in only 2 per cent of Rimpau's<sup>13</sup> cases of "field fever" caused by *Leptospira grippotyphosa*.

Although the first proved cases of Weil's disease in Great Britain<sup>14</sup> and in the United States<sup>15</sup> were reported in the same year, 1922, subsequent reports give the impression that the disease is much more common in Great Britain than it is here, which there is reason to doubt. For example, between 1922 and 1939, 248<sup>16</sup> proved cases have been recorded by British observers but only about twenty-three in this country. The large number of cases recognized abroad may be partly attributed to a greater interest in the disease



*Leptospira icterohaemorrhagiae* in liver of a guinea pig inoculated with patient's blood. Levaditi's stain,  $\times 1,000$ .

there and to the recognition of the milder, nonicteric forms of the disease. The latter point is of especial importance, and because of it it is necessary to revise our criteria of the "classic" case of Weil's disease. It is most likely that the striking, easily recognized forms with jaundice, hemorrhage and fever are only the severest forms of an infectious disease which is usually mild and therefore unrecognized. It is probable that, as in other infectious diseases, the mild forms far outnumber the severe ones. This being true, Weil's disease may be arbitrarily graded into (a) subclinical or mild ambulatory forms, (b) moderately severe icteric or non-icteric forms and (c) severe, often fatal, forms with jaundice and bleeding. It is evident that without the use of serologic, cultural or other tests the mild forms may be mistaken for other diseases, especially influenza,

since an acute onset with a chill, fever, pain in the limbs, headache and conjunctival injection are usually present.

We believe that the leptospiroses are much more common in the United States than is generally believed. Cases have been reported from many isolated parts of the country, most recently from New Jersey and Pennsylvania<sup>17</sup> and from California,<sup>9</sup> where *Leptospira canicola* has been found in dogs. No doubt in many cases the diagnosis is missed, especially if visible jaundice is absent, and even when the diagnosis is made the disease, not being a "reportable" one, is usually not listed in vital statistics. We know of a number of unreported cases in Philadelphia.

Weil's disease affects chiefly workers in certain occupations. For example, in Great Britain<sup>18</sup> the disease occurs most often among fish handlers, coal miners and sewer workers, each of whom work in environments often infested with rats, the natural source of the disease. Bathing in water presumably polluted with rat excreta is the fourth most common mode of infection in Great Britain,<sup>19</sup> and, according to Walch-Sorgdrager,<sup>10</sup> 78 per cent of patients in Holland were infected in this manner. Schüffner<sup>20</sup> stresses the role of struggling and inhalation of water incident to submersion or of using the "crawl" stroke in swimming as factors favoring infection. Infection may also be acquired by drinking contaminated water, as illustrated by the outbreak of Weil's disease in Lisbon in 1931.<sup>21</sup>

To emphasize the danger of bathing in possibly contaminated water, a small outbreak which occurred in July 1939 is described. Seven young men swam in a public bathing pool formed by a dam in a creek near Philadelphia. The pool was adjacent to cattle barns and refuse pits which were infested with rats. From four to twelve days after swimming, each of these men became sick in varying degrees of severity.

#### REPORT OF CASES

Of the seven patients, two were sick enough to require hospital care and one of these died. Of the five patients with mild attacks, two were obliged to spend several days in bed but the other three were ambulatory.

CASE 1.—J. C. had chills followed by fever and intense frontal headache six days after swimming. Malaise, weakness and pains in the legs were severe enough to require a week's rest in bed. There was anorexia but no jaundice or vomiting. Convalescence was rapid.

CASE 2.—V. P. was taken with malaise, general weakness, aching and anorexia one week after swimming. There was no jaundice. Recovery was rapid after two days spent in bed.

CASES 3, 4 and 5.—The symptoms were those of chilliness, headache, weakness, anorexia and pains in the legs for from several days to a week. The symptoms are indeed not specific but are the same as those of the cases of mild involvement studied in Europe. The patients were ambulatory. The same symptoms were also present in the two cases of severe involvement but were much more pronounced and accompanied with jaundice, bleeding and high fever.

CASE 6.—E. Z. aged 24 (record by courtesy of Dr. E. P. Reif) was admitted to the Methodist Episcopal Hospital July

12. Joerdens, J.: Beitrag zur Klinik und spezifischen Serumtherapie des Feldfiebers, München. med. Wchnschr. 85: 1979-1981 (Dec. 23) 1938.

12a. Babudieri, B.: Rend., Inst. di san. pub. 2: 755 (Dec.) 1939.  
13. Rimpau, W.: Weiteres zur Epidemiologie des Feldfiebers in Südbayern, München. med. Wchnschr. 85: 1977-1979 (Dec. 23) 1938.

14. Manson, Bahr, P., Wenyon, C., and Brown, H.: A Case of Weil's Disease Occurring in London, Lancet 2: 1056-1059 (Nov. 18) 1922.

15. Wadsworth, Augustus; Langworthy, H. Virginia; Stewart, F. Constance; Moore, Anna C., and Coleman, Marion B.: Infectious Jaundice Occurring in New York State, J. A. M. A. 78: 1120-1121 (April 15) 1922.

16. Davidson, L. S. P., and Smith, J.: Weil's Disease in the North East of Scotland: An Account of One Hundred and Four Cases, Brit. M. J. 2: 753-757 (Oct. 14) 1939.

17. Annual Report of the Surgeon General of the Public Health Service of the United States for the Fiscal Year 1939, pp. 9 and 67.

18. Alston, J. M., and Brown, H. C.: The Epidemiology of Weil's Disease, Proc. Roy. Soc. Med. 30: 741-756 (April) 1937.

19. Alston, J. M., in Report of Proceedings of the Third International Congress of Microbiology, New York, Sept. 2-9, 1939, New York, the Congress, 1940, p. 278.

20. Schüffner, W. A. P.: Recent Work on Leptospirosis, Tr. Roy. Soc. Trop. Med. & Hyg. 28: 7-37 (June) 1934.

21. Jorge, Ricardo: Une épidémie à Lisbonne d'ictère hémorragique d'origine hydrique contracté per os: Nosologie, bactériologie, et étiologie, Bull. Office internat. d'hyg. pub. 2-4: 88-117 (Jan.) 1932.

24, 1939. Four days before admission and four days after swimming he had a shaking chill followed by malaise, weakness and fever. He was somewhat better the following morning, although his temperature was 38.3 C. (101 F.) On admission on the fourth day of his illness he complained of severe pain in the left side of the face radiating to the forehead, malaise, weakness and a sense of oppression in the chest.

The patient was well developed and well nourished and was acutely ill. His face was flushed and his throat was injected. Breath sounds were suppressed, resonance was impaired and rales were present in the lower portion of the right lung. On the left side a few crackling rales were heard at the base of the lung. The heart rate was rapid and regular. The abdomen was distended but the liver and spleen were not felt. Reflexes were physiologic. The hemoglobin content measured 76 per cent and the erythrocytes numbered 3,800,000 and the leukocytes 18,600. There were albuminuria, hematuria and bile in increased amounts in the urine. The direct van den Bergh test gave a positive reaction and the icterus index was 102. The blood urea nitrogen was 120 mg. and the Wassermann reaction was negative. A roentgenogram of the chest revealed patches of increased density over both lung fields, interpreted as pneumonia.

During the ensuing eight days the patient became worse. The jaundice, hematuria and nitrogen retention increased. Slight nuchal rigidity appeared and he vomited bloody material on several occasions. There was tenderness over the liver, which became palpable from one to two fingerbreaths below the costal border. During this time the temperature declined by lysis to normal, remaining so for four days, and then rose again to 40.5 C. (105 F.), with daily fluctuations for the next three weeks, during which the patient gradually improved with the jaundice and hematuria diminishing. He left the hospital well except for slight jaundice five weeks after admission.

**CASE 7.—History.**—A. N., aged 26, went to bed feeling chilly and weak six days after he had been swimming. The next day he felt better and got up but soon returned to bed. There were anorexia, constipation and fever. He was admitted to the hospital on the fourth day of his illness complaining of severe headache, pains throughout the body, weakness and cough.

The patient was well developed and well nourished; he was dyspneic, cyanotic and intensely jaundiced. The temperature was 38.9 C. (102 F.), pulse rate 122, respiratory rate 36, blood pressure 122 systolic and 78 diastolic. The conjunctivas were injected, the nose was bleeding and there were excoriations along the nasal septum. Over the right lower and middle lobes of the lung the breath sounds and resonance were impaired. Tactile fremitus and vocal resonance were increased. There were medium and fine rales extending to the infraclavicular region and to the scapula posteriorly. The heart was slightly enlarged with a systolic murmur at the apex. There was areflexia in the lower extremities and distal hyperalgesia. The hemoglobin measured 50 per cent, the erythrocytes numbered 2,600,000 and the leukocytes 28,000. There were heavy albuminuria and hematuria, and urobilinogen was positive in a dilution of 1:400. The serum bilirubin was 18.2 mg. with a positive direct van den Bergh reaction, with 70 per cent bromsulphalein dye retention. The Wassermann reaction was negative. A roentgenogram of the chest revealed increased density over the right middle and lower lobes of the lungs, interpreted as pneumonia.

The patient rapidly became worse; jaundice and hematuria increased. Evidence of consolidation spread to the left lung. Subconjunctival hemorrhages appeared, the temperature decreased and the patient died on the seventh day of illness.

The chief abnormalities noted by Dr. M. M. Lieber post mortem were generalized icterus, a peculiar irregular type of consolidation due to extensive hemorrhage in both lower lobes of the lungs, splenomegaly, acute hepatitis and acute ulcerative gastroenteritis. Histologically there was leptospirosis of the liver and kidneys.

**Biologic Study.**—On the sixth day of illness the patient's blood and urine were examined by the dark field method for the presence of leptospiras but none were found. At the same

time 5 cc. of citrated blood of the patient was injected intraperitoneally into each of four guinea pigs. Two animals died soon after but the other two developed a temperature of 40.5 C. (105 F.) six days later, became jaundiced on the seventh day and died on the ninth. *Leptospira icterohaemorrhagiae* was found in sections of the liver and kidneys when stained by Levaditi's method, as shown in the accompanying illustration. Blood taken from these animals during their illness caused similar disease when injected into fresh guinea pigs. *Leptospiras* were cultivated from the blood when incubated in Manteufel's medium.

Attempts were later made to prove the diagnosis of Weil's disease in the six other members of the party who had been sick at the same time. Blood was taken from each about fifty days after his attack and sent to Dr. Packchianian of the National Institute of Health, who tested the serum for the presence of agglutinins for *Leptospira icterohaemorrhagiae*. Specific agglutinins were present in a titer of 1:10,000 in case 6 but were absent in serum from the patients who had had mild attacks.

#### COMMENT

Although proof of Weil's disease was not established in the mild cases of the outbreak, it is highly probable that all the men suffered from the same disease. They swam together in a pool likely to have been polluted with rat excrement, they became sick at about the same time afterward and most of their symptoms were similar except in the degree of severity. The fact that no agglutinins were demonstrable in the blood of the mildly sick patients, fifty days later, although failing to prove the diagnosis, does not detract from it. Rimpau has shown that, as in other infections, specific agglutinins may never develop or they may disappear within a few weeks, particularly in mild cases of field fever. We requested permission to catch some of the rats in the vicinity of the pool, but the owner of the premises was loath to give it, so that studies could not be made.

#### SUMMARY

In July 1939 seven young men bathing in a stream probably polluted by infected rats contracted an acute infectious disease in varying grades of severity. Five were affected mildly and two were severely sick, one of whom died. Cultural studies in the fatal case and serologic evidence in the other severe case proved a diagnosis of leptospirosis icterohaemorrhagica. Clinical and epidemiologic evidence favored a similar diagnosis in the mild cases, although serologic confirmation was not obtained.

The possible danger of contracting leptospirosis by bathing in ponds likely to be polluted by rats and of drinking polluted water should be kept in mind.

---

**Development of Cold Storage.**—A schoolteacher, Benjamin Nyce, is to be credited with the invention of a satisfactory system of cold storage. In 1857 he erected near his home a small insulated building divided into two compartments by a horizontal sheet of iron. The upper compartment was filled with ice, the lower used for the storage of provisions, and all important facilities for adequate ventilation and the absorption of excess moisture were provided. This device—in essence a gigantic icebox—was patented by Nyce in 1858. So successful was his plan and so large were the profits in the handling of out of season fruits that use of the method spread widely. Substitution of mechanical refrigeration for natural ice in the 1870's made storage on a large scale possible, and by the close of the century the number of storage houses for fruit and vegetables located in the smaller cities and towns was increasing rapidly.—Cummings, Richard Osborn: *The American and His Food*, Chicago, University of Chicago Press, 1940.

# THE USE OF PHYSICALLY INDUCED PYREXIA AND CHEMOTHERAPY

IN THE TREATMENT OF SUBACUTE  
BACTERIAL ENDOCARDITIS

WILLIAM BIERMAN, M.D.

AND

GEORGE BAEHR, M.D.

NEW YORK

An elevation of temperature increases the intensity of chemical reactions. This has been demonstrated in vivo by the improved therapeutic results following the use of elevation of body temperature when sulfanilamide is employed to kill that relatively fragile bacterium the gonococcus.<sup>1</sup> It has been demonstrated in vitro for the hemolytic streptococcus by White,<sup>2</sup> who showed that the bacteriostatic power of sulfanilamide is about one hundred times greater at 39 C. than at 37.2 C.

We have had the opportunity of applying a combination of chemotherapy (sulfanilamide or sulfapyridine) and physically induced elevation of body temperature to cases of subacute bacterial endocarditis. Out of 16 patients each of whom received six or more bouts of temperature elevation in conjunction with medication, but 2 have made recoveries. In still another typical case the blood cultures which were consistently positive for *Streptococcus viridans* have been negative for the past four months. This patient seems also to have recovered. However, this period of follow-up is too short to permit us to include him in our present series.

This record is certainly not a brilliant one. However, in a disease which is usually fatal, the fact that two recoveries did occur challenges attention. Libman<sup>3</sup> states that spontaneous recovery occurs in 3 per cent of cases. In contrast, the results in our series are statistically better than this, but the number of our patients is too small to be challenging. Long and Bliss<sup>4</sup> have reported five apparent cures in 60 cases following the use of sulfonamide therapy alone. In 22 of our own cases there has been one recovery following the use of chemotherapy without pyrexia.

Because of their unusual therapeutic sequelae, a description of our 2 cases in which recovery occurred may be of interest:

**CASE 1.**—A man aged 32 suffered from subacute bacterial endocarditis due to *Streptococcus viridans*. Five weeks before admission to the hospital, he noted the development of sore throat and severe right frontal headache. The headache and sore throat abated after a few days, but the fever continued. The temperature was noted to be at about 100 F. in the morning, reaching 101-102.5 F. during the evening.

The patient was well developed and well nourished. He did not appear very ill. Examination of the heart revealed no enlargement. The sounds were of good quality; there was a

blowing systolic murmur to the left of the sternum over the mitral area which was not well transmitted to the axilla. The blood pressure was 124 systolic and 70 diastolic. Abdominal examination was entirely negative. The liver and spleen were not felt. A moderate degree of clubbing of the fingers was noted. There were no petechiae, and examination of the fundi revealed no hemorrhages. On admission, hemoglobin was 85 per cent, white blood cells 13,500, polymorphocytes 79 per cent, of which 14 per cent were nonsegmented forms, lymphocytes 14 per cent, monocytes 7 per cent. No macrophages were seen in a smear of blood from the ear lobe. Sedimentation time was 55 minutes. Admission urine showed only a faint trace of albumin and an occasional white blood corpuscle. However, microscopic examination of the sediment of later urine showed occasional red blood cells and at times a few granular and cellular casts. An electrocardiogram showed a left ventricular preponderance with no abnormality of the ventricular waves to suggest myocardial damage. During the first week in the hospital the patient's temperature ranged between 99 and 101.8 F. Because of the presence of clubbing of the fingers and a systolic murmur at the apex, the diagnosis of subacute bacterial endocarditis was considered and blood cultures were taken. This impression was confirmed by the finding of *Streptococcus viridans*, two colonies per cubic centimeter, on the initial blood culture taken on Sept. 18, 1938, with a second report of *Streptococcus viridans* fifteen colonies per cubic centimeter on September 21. Although previous therapeutic attempts in this disease had not met with any success, it was decided to treat the patient with radiotherapy and then with a combination of sulfanilamide and hyperpyrexia. Accordingly, on September 30 radiotherapy was instituted and during the ensuing eight days the patient received six exposures, totaling 2,400 roentgens directed over the precordium. No subjective or objective improvement could be discerned during or immediately after this course of treatment. The temperature continued to range between 100 and 102.6 F. The urine continued to show the presence of red blood cells.

After the initial radium treatment the patient complained of a sudden onset of pain in the left temporal region. Over an anterior branch of the left temporal artery a tender, raised, slightly reddened area was noted. There was no distal discoloration, but no pulsation could be felt in the distal portion of the artery. It seemed most likely that this was either an embolization of a small arterial branch or a mycotic aneurysm. This lesion subsided with the application of wet dressings over the involved area. On October 7, after the last radium treatment, the patient complained of a sudden marked pain in the left side of his abdomen associated with nausea. The abdomen was soft throughout but there was tenderness on deep pressure, which was most marked at the left costovertebral angle. Although urinalysis following this episode showed only two to four red blood cells per high power field, a renal infarction was considered the etiologic factor for this pain. Again on October 11 the patient complained of generalized abdominal pain associated with nausea, and following this he vomited some undigested food. Simultaneously the temperature rose to 104.4 F. Examination revealed only moderate distention with deep diffuse tenderness. An embolic phenomenon was considered this time, perhaps to a small division of a mesenteric artery. On October 12, treatment with sulfanilamide was instituted and a total of 66 Gm. was given over a period of eleven days, a blood concentration of 9 mg. per hundred cubic centimeters of sulfanilamide being attained. During this period the patient appeared much more ill and his temperature ranged to higher levels, frequently reaching 104 F. Because of what appeared to be a toxic effect of sulfanilamide, and because of a drop of hemoglobin from 80 per cent to 65 per cent, the latter treatment was discontinued on October 22. On October 14, hyperpyrexia was started, and the patient received nine such treatments. The temperature was raised from 104 to 105.6 F. and was maintained at that level for between three and six hours. After discontinuance of the sulfanilamide the temperature ranged to lower levels, usually varying between 99 and 101 F. On November 1 a blood culture showed the presence of *Streptococcus viridans* in two flasks, and three colonies

From the Departments of Physical Therapy and Medicine of the Mount Sinai Hospital.

1. Ballenger, E. G.; Elder, O. F., and McDonald, H. P.: Sulfanilamide and Thermotherapy in Gonococcal Infections: Preliminary Report, *J. A. M. A.* 109: 1037 (Sept. 25) 1937. Kendall, H. W.; Rose, D. L., and Simpson, W. M.: Artificial Fever Versus Combined Fever-Chemotherapy in Gonococcal Infections Refractory to Sulfanilamide, read before the annual meeting of the American Congress of Physical Therapy, Cleveland, Sept. 4, 1940.

2. White, H. J.: The Relationship Between Temperature and the Streptococidal Activity of Sulfanilamide and Sulfapyridine in Vitro, *J. Bact.* 38: 549 (Nov.) 1939.

3. Libman, Emanuel: A Further Report on Recovery and Recurrence in Subacute Bacterial Endocarditis, *Tr. A. Am. Physicians* 48: 44, 1933.

4. Long, P. H., and Bliss, Eleanor A.: The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds, New York, the Macmillan Company, 1939.

were seen on the blood plate. Hyperpyrexia was continued from October 14 to November 8, at which date the last treatment was given. On November 12 a blood culture showed no growth, and subsequent blood cultures taken on November 17 and 25 and again on December 2 were also sterile. Simultaneously there was a marked improvement in the general condition of the patient; his temperature returned to normal levels, the hemoglobin rose from 65 to 90 per cent, there were no further embolic phenomena, and red cells disappeared from the urine. The cardiac murmur remained unchanged. Clubbing of the fingers, which was previously noted, completely disappeared within three weeks after the blood became sterile and the temperature normal. The patient has now been well and at work for more than two years.

**CASE 2.**—A girl aged 19 years had subacute bacterial endocarditis due to the bacillus of influenza. About two and one-half weeks before her admission to the hospital she had a severe chill, which lasted for one half hour and was followed by a temperature elevation to 104 F. accompanied by malaise, anorexia and a dull backache. She was then well for several days until six days before admission, when she again had a shaking chill. Following this she had an irregular temperature between 101 and 103 F. without localizing symptoms.

The patient was asthenic, poorly developed and nourished, sallow but not acutely ill. There was no cardiac enlargement. There was a low pitched, short, systolic murmur, not transmitted. No thrills were present. The sounds were of good quality; the second pulmonic sound was louder than the second aortic. The blood pressure was 110 systolic and 70 diastolic. The abdomen was soft and scaphoid. Loops of the bowel were easily palpable. The spleen was moderately firm, nontender and palpable two fingerbreadths from the left costal margin on deep inspiration. The hands were moist. Slight pain was experienced on motion of the right wrist. Hemoglobin was 68 per cent; the leukocyte count was 12,200, with segmented cells 68 per cent, nonsegmented 6 per cent, lymphocytes 24 per cent, monocytes 2 per cent. The sedimentation time was forty minutes. An electrocardiogram showed no abnormality. The urine was normal. Blood agglutination for typhoid and paratyphoid and *Brucella melitensis* was likewise negative.

During the first two weeks of her stay in the hospital, the patient's temperature ranged irregularly between 100 and 104 F. The pulse was relatively slow, averaging 90. The respiratory rate was 22. The body weight was 97 pounds (44 Kg.). The first three blood cultures revealed no growth but the fourth, taken when the temperature was 104 F., was positive for the influenza organism after two days' incubation under either aerobic or anaerobic conditions or under carbon dioxide. This organism needed blood, as was shown by its failure to grow in

the highest number of white blood cells recorded, 17,200, segmented polymorphocytes 61 per cent, nonsegmented 19 per cent, lymphocytes 15 per cent, monocytes 5 per cent. The patient was given numerous transfusions, despite which the hemoglobin did not rise above 80 per cent. During this period the systolic apical murmur became somewhat louder. A few hemorrhagic spots appeared on the fingers. These were interpreted as Janeway nodes. They were nontender and disappeared in a few days. The spleen became somewhat larger, and a few petechiae were noted in the buccal mucous membrane. At

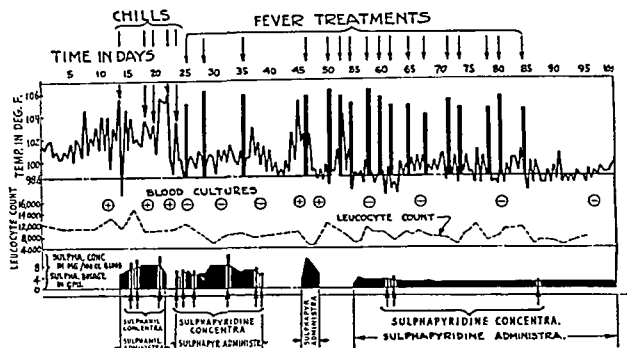


Fig. 2.—Course in case 2.

another period slight soreness of the throat was complained of, but there were no objective lesions. The only toxic manifestations to the administration of this drug were some nausea and occasional vomiting and marked cyanosis. Because of failure of sulfanilamide to affect the course, it was decided to switch to sulfapyridine 6 Gm. daily. This was later changed to 3 Gm. and a total of 99.5 Gm. was given in two and one-half weeks. During this time three physically induced fever treatments were administered. Two blood cultures drawn during this period were negative. The temperature ranged between 99 and 101 F. However, a week after the drug and the fever treatments were stopped, the culture again became positive and the temperature varied between 101 and 105 F.

In view of the fairly satisfactory response with the use of sulfapyridine and fever treatments previously, it was decided to start this regimen again. After several days, however, the white blood cell count dropped to 4,700, the temperature in the meantime falling to normal. The drug was discontinued for six days, but the fever applications were continued. The administration of sulfapyridine was started again, 2 Gm. daily, the blood count being followed carefully. The response to this regimen was excellent. The temperature fell to normal limits and varied between 101.5 and 98 F. for the next four weeks. In the last two weeks of her hospital stay, the highest temperature was 99.8 F. Two blood cultures during this period revealed no growth. The white blood cell count remained 8,000 with normal differential. The hemoglobin was kept to 75 per cent by occasional blood transfusions. A blood level of 3 mg. per hundred cubic centimeters of sulfapyridine could be maintained with this small dosage. In all, 99 Gm. of sulfapyridine was given during a six weeks period. Appetite was good and there was a gradual gain in weight. Embolic phenomena were no longer noticed. The spleen receded in size but was still palpable at the time of discharge. The systolic cardiac murmur almost entirely disappeared. The generalized lymphadenopathy was no longer present, and the urine showed no abnormalities.

Early in the course of sulfapyridine administration, when the temperature fell to within relatively normal limits, it was decided to institute hyperthermia to increase the bactericidal activity of the blood and tissue. Accordingly the patient was given a course of sixteen sessions during which the body temperature was raised to between 105 and 106 F. for five hours. She withstood this therapy well. It was felt that the hemopoietic stimulating effect of hyperthermia contributed to the maintenance of a relatively normal blood count. About two weeks before discharge, the patient developed a left lower lobe pulmonary infarct, and roentgen examination of the chest

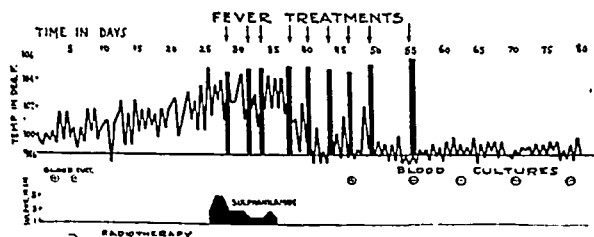


Fig. 1.—Course in case 1.

unenriched mediums. It reduced nitrate to nitrite and had the typical morphologic appearance of the influenza group. On primary culture it agglutinated in a dilution of 1:28 with stock anti-influenza serums, but after several transplants the agglutinability disappeared. The patient's serum and that of another patient with endocarditis due to a similar organism were extremely potent in agglutinating this organism. Titers higher than 1:1,000 were obtained.

The patient was started on sulfanilamide 6 to 8 Gm. daily for ten days. There was but little effect on the temperature curve. Blood cultures drawn when the blood sulfanilamide level was as high as 11 mg. per hundred cubic centimeters were recorded positive. The blood count at this time revealed

shortly after this revealed some elevation of the left leaf of the diaphragm and the presence of a small amount of fluid. At no time did the electrocardiogram reveal any definite abnormality. Several urine cultures did not show significant organisms; however, on two occasions *Bacillus influenzae* was recovered from a throat culture. Neither one of these was taken during a course of sulfapyridine. Roentgen examination of the paranasal sinuses failed to reveal any abnormality.

After discharge from the hospital the patient continued to take maintenance doses of sulfapyridine, 0.5 Gm. every six hours. Blood counts were taken periodically. During the month following her discharge from the hospital she gained 14 pounds (6.4 Kg.). There were no symptoms of drug intolerance, infection or diminished cardiac reserve. Blood cultures were negative. The administration of the drug was discontinued on June 4, 1940. Blood cultures continued negative and have remained so. She has been well for ten months. There is only the faintest trace of a systolic murmur at the apex. The spleen is barely palpable. There are no embolic phenomena. She indulges in active physical exercise.

#### TECHNIC

The administration of physically induced pyrexia to patients suffering from subacute bacterial endocarditis presents special difficulties, as their cardiovascular system may show evidence of considerable damage. They therefore require particularly close watching. As in many instances they come for treatment with an elevation of temperature (100 to 103 F.) it is unnecessary to use as much convective and conductive heating as in the treatment of other conditions. Otherwise the systemic temperature will climb too rapidly and to too high a level. The use of large doses of sulfanilamide before and during the pyrexia treatments may cause the patient to become a bluish gray, thus making it difficult to recognize the onset of cyanosis. The pulse rate is usually rapid, varying from about 130 to 160 beats per minute. In spite of the administration of morphine sulfate, patients are frequently very restless. Nausea, circumoral pallor and very rapid respiration are symptoms which may develop even though the temperature elevation be at a comparatively low level. These symptoms may be due to the severe cardiac involvement. We have also observed the development of a rash during the treatment or on the day following. This rash covers the entire body or is localized to the chest, hands and arms. Although the treatments are uncomfortable and require the use of sedation, it was of interest to note that the 2 patients who survived were not disturbed by the treatments given initially. On the contrary, they asked that the pyrexia sessions be administered because they felt so much more comfortable during and after them. Subsequently in the course of these treatments they began to object to them as do other patients.

#### COMMENT

The results achieved in these 2 cases indicate to us the need for the further study of this method of treatment for subacute bacterial endocarditis. The problems which should be solved include the determination of the height and duration of the optimum temperatures to be induced and the optimum concentration of the drug in the blood. It has been shown that great variations in blood concentration occur which bear no exact relationship to the dosage of the drug.<sup>5</sup> Also the concentration of the drug differs in different parts of the body, having been found to be highest in the lungs, skin and kidneys. The initial decrease in systemic temperature and the negative cultures following the

positive ones in the second case would tend to show that a bacteriostatic influence had been exerted on the blood by the treatment. It is possible that the verrucous deposits on the heart valves continued to harbor the micro-organisms which were not killed and which subsequently caused the blood cultures to become positive. The relatively avascular status of the verrucous deposits makes it difficult to influence these regions chemically. The induced pyrexia may assist in making chemotherapy more effective in this region.

In the second case it is of interest to observe that the chills ceased after the inauguration of the physically induced pyrexia. Following the fever treatments, the systemic temperature usually falls to a relatively low level from which it gradually reascends. We have observed this to occur also in cases of gonorrhea when our treatment has not been adequate to kill all the organisms. The induced fever of itself produces a leukocytosis.<sup>6</sup> This makes it of particular value in the treatment of leukopenia, which so frequently occurs after the ingestion of these drugs. Thus in one instance a white blood cell count of 4,950 was raised to 6,800 by a relatively mild pyrexia session.

In 1933 one of us applied physically induced pyrexia (without additional chemotherapy) to a patient suffering from subacute bacterial endocarditis. At the time the patient was actively embolizing. Following the second treatment, showers of numerous emboli caused an exitus. Postmortem examination showed the body organs to be filled with numerous fresh and old emboli. No deaths occurred as a result of the fever treatments in our present series of cases.

Krusen and Bennett<sup>7</sup> reported 6 cases unsuccessfully treated with sulfanilamide and hyperthermia. Ferderber,<sup>8</sup> applying this combined therapy to 3 patients, reports two recoveries. Solomon<sup>9</sup> has observed five apparent recoveries out of a series of 17 patients after a combination of sulfonamide and pyrexia induced by the intravenous injection of killed typhoid bacteria. In all reported series of cases treated with any of the sulfonamide drugs, with or without pyrexia, transient periods of apparent recovery may occur during which the temperature may remain low and the blood culture be negative. Unless the patients have remained well for many months or years, it is unwarranted to regard them as cured.

#### CONCLUSION

Our experience would indicate that physically induced pyrexia enhances the value of chemotherapy in the treatment of subacute bacterial endocarditis. Of 2 cases reported, one was due to *Streptococcus viridans* and one to *B. influenzae*, in which recovery occurred and the patients have been well for two years and for ten months respectively. A third patient, with *Streptococcus viridans* endocarditis, has been well for four months, but this interval is still too brief to describe as a cure. In 13 cases the disease was influenced by the therapy only temporarily or not at all. These clinical results support the *in vitro* observations of White that the effectiveness of the sulfonamide drugs is materially enhanced at sustained higher elevations of temperature.

471 Park Avenue—110 East Eightieth Street.

6. Bierman, William: The Effect of Hyperpyrexia Induced by Radiation upon the Leukocyte Count. *Am. J. M. Sc.* 187:545 (April) 1934.

7. Krusen, F. H., and Bennett, R. L.: Unsuccessful Treatment of Subacute Bacterial Endocarditis with Combined Fever and Sulfanilamide Therapy. *Proc. Staff Meet., Mayo Clin.* 15:328 (May 22) 1940.

8. Ferderber, M. B.: Personal communication to the authors.

9. Solomon, H. A.: Subacute Bacterial Endocarditis. *New York State M. J.* 41:45 (Jan. 1) 1941 and personal communication to the authors.

5. Bullowa, J. G. M.; Ratish, H. D.; Davidson, Arnold, and Lehair, Constance: The Administration of Sulfapyridine and Its Congeners in Pneumonias. *New York State J. Med.* 40:1450 (Oct. 1) 1940.



## Clinical Notes, Suggestions and New Instruments

### FATAL AGRANULOCYTOSIS FROM SULFATHIAZOLE

POTNAM C. KENNEDY, M.D., AND MAXWELL FINLAND, M.D.  
BOSTON

The chief objective in the search for new chemotherapeutic agents is to find drugs which have both greater effectiveness and lower toxicity. Sulfathiazole, according to some observers, presents a number of favorable features in these respects when compared with other sulfonamides that are in common use. One of the features usually mentioned is that acute agranulocytosis resulting from its use has not been reported.<sup>1</sup> We present here a case in which this complication occurred and proved fatal.

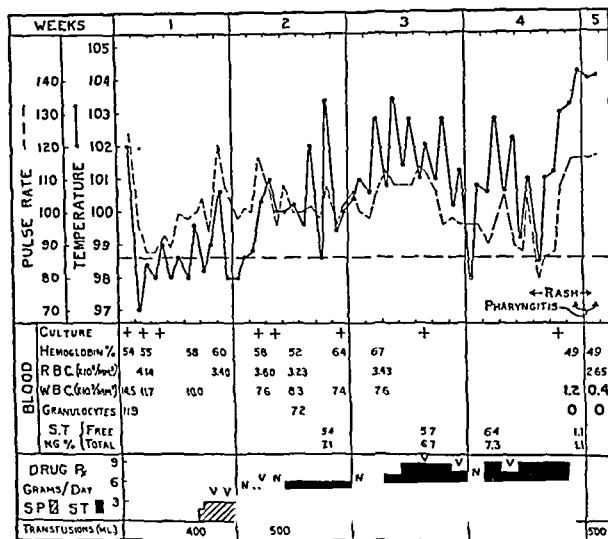
#### REPORT OF CASE

**History.**—An American woman aged 38, a housewife, was admitted to the Boston City Hospital on June 23, 1940. She had been in good health until seven weeks previously, when she began to have drenching sweats at night and a spiking temperature reaching 103 to 104 F. daily, which continued to the time of entry. She had occasional chills during this time, and her physician kept her in bed. She lost 22 pounds (10 Kg.) up to the time of entry. For a few days she had suffered sharp, stabbing pain in the left side of the upper part of the abdomen (in the region of the spleen) and in the left side of the lower portion of the chest, both pains becoming worse on inspiration. Just before entry, her left shoulder and the upper part of her left arm became painful and she experienced some urgency of urination. She remembered vaguely having had a slightly swollen ankle during the previous winter but could recall no details. There was no other previous history of swollen or painful joints, rheumatic fever or cardiac symptoms. The patient had never been treated with sulfonamides before. She had one child, aged 9 years, who had suffered an injury at birth and was mentally retarded. Her past history, family history and marital history were otherwise irrelevant.

**Physical Examination.**—The patient was fairly well developed but thin and of small stature. At the time of admission she had no respiratory distress but complained of pain in the upper portion of her left arm and left shoulder on changing her position. The skin was pale, but warm and moist. The veins of the neck were slightly distended, and there were a few small, nontender cervical nodes on both sides. The heart was somewhat enlarged to the left, with the left border of dullness in the fifth intercostal space 11 cm. to the left of the midsternal line and the maximum impulse felt in the fourth intercostal space 8 cm. from the midsternal line. The heart sounds were regular and of good quality, the pulmonic second sound being sharp and metallic and much louder than the aortic second sound. There was a blowing systolic murmur and a low-pitched rumbling diastolic murmur at the apex, transmitted to the left axilla. A systolic murmur was also heard over the base of the heart and was loudest over the second interspace on the left side. The liver could be felt at the right costal margin on deep inspiration. There was definite clubbing of the fingers. The rest of the physical examination at this time gave negative results. In particular, no petechiae were seen, nodules were not felt, the joints were not swollen or tender, the lungs were entirely clear, the spleen was not felt, there was no edema of the extremities and the reflexes were normal and equal bilaterally, although slightly hyperactive.

**Laboratory Data.**—The most significant data are shown in the accompanying chart. Other relevant findings included the following: A catheterized specimen of urine on admission showed 1 to 2 red blood cells and 8 to 10 white blood cells with occasional clumps but no casts and negative reactions for sugar and albumin. Culture of this specimen of urine yielded

enterococci and *Staphylococcus aureus*. Numerous subsequent specimens of urine showed either no albumin or the slightest trace, but no formed elements were seen on microscopic examination of the sediments. The blood smear on admission showed a differential leukocyte count of 82 per cent polymorphonuclear neutrophils, 16 per cent lymphocytes and 2 per cent monocytes; the red blood cells were slightly hypochromic and varied somewhat in size, and the platelets appeared normal. Subsequent differential leukocyte counts were essentially the same until July 20 and 21, when there were no granulocytes seen in the blood smears, only lymphocytes and rarely a monocyte. The blood nonprotein nitrogen level was 30 mg. per hundred cubic centimeters on admission and 49 mg. two days later. The blood Hinton reaction was negative. A roentgenogram of the chest showed the heart slightly enlarged to the right and left, the shape being consistent with mitral stenosis. There was slight mottling of both lung bases, interpreted as congestive changes. An electrocardiogram taken on the day after admission showed sinoauricular tachycardia; the PR interval was 0.16, with low voltage of QS complexes (0.6 millivolts); the T wave in leads 1 and 2 was low, in lead 3 inverted and in lead 4 diphasic; there was preponderance of the left ventricle. These findings are interpreted as consistent with myocardial disease.



A case of acute agranulocytosis resulting from sulfathiazole therapy. Blood culture ++ positive for *Streptococcus viridans*; granulocytes = total number in thousands per cubic millimeter; S. T. = sulfathiazole; S. P. = sulfapyridine; N = nausea; V = vomiting. Only the doses of drugs actually taken by the patient are charted.

**Hospital Course and Treatment** (see chart).—With the history and the results of physical examinations and with reports of *Streptococcus viridans* in repeated blood cultures, a diagnosis was made of subacute bacterial endocarditis superimposed on rheumatic heart disease with mitral stenosis. On the fifth day in the hospital, treatment with sulfapyridine (1 Gm. every four hours) was started, but because of the severe nausea and vomiting sulfathiazole was substituted and given at first in the same dosage and, beginning in the middle of the third week, in 1.5 Gm. amounts every four hours. A number of doses were refused from time to time by the patient, and the nausea and vomiting continued intermittently. Her appetite remained poor throughout, but she maintained a good intake of fluids. The patient was also given three transfusions, as noted in the chart. The first of these was followed by a chill of moderate severity and by a brief period of pulmonary congestion and edema which improved after the application of tourniquets to the extremities and the administration of oxygen and small doses of morphine. On the tenth day, a few petechiae were noted below the angles of the scapulas and on the second finger of the right hand. On the nineteenth day, there was tenderness in the region of the spleen and a friction rub was heard over it. At that time there was also a shower of petechiae seen over the left breast.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), and the Mallory Institute of Pathology, Boston City Hospital, and the Department of Medicine, Harvard Medical School.

1. The literature concerning sulfathiazole has recently been reviewed by Sprink, W. W., and Hansen, A. E.: Sulfathiazole: Clinical Evaluation, *J. A. M. A.* 115: 840-847 (Sept. 7) 1940.

The course of the temperature, pulse rate and blood content is shown in the chart. On the twenty-fifth day a few small papules appeared on the forearms. These increased slowly in size and number on both forearms and elbows, and a few faintly red, tender subcutaneous nodules 5 to 10 mm. in diameter appeared three days later on the knees and anterior surfaces of the lower legs. On the twenty-eighth hospital day, after several days when blood counts had not been done, the leukocyte count was found to be 1,200 and no granulocytes were seen in the smear. Sulfathiazole therapy was stopped as soon as this was learned, and the patient was given a blood transfusion, 10 cc. of liver extract and 30 cc. of pentnucleotide intramuscularly, and an additional 1,500 cc. of physiologic solution of sodium chloride intravenously. The throat at this time showed a few pus-filled crypts in the right tonsil, and later ulcerations on the tonsils, which increased without any marked surrounding inflammatory reaction. Numerous small petechiae also appeared on the trunk. The next day, while the patient was apparently sleeping peacefully, she suddenly gasped and died.

The clinical diagnoses were subacute bacterial endocarditis (*Streptococcus viridans*) of the mitral valve; splenic infarct; rheumatic heart disease with cardiac enlargement, mitral stenosis and regurgitation; acute agranulocytosis due to sulfathiazole; sulfathiazole dermatitis, and secondary hypochromic anemia.

**Significant Observations at Autopsy.**<sup>2</sup>—The body weight was 36.5 Kg. The head was not examined. The heart weighed 260 Gm. and had three endocardial vegetations: the largest was on the left auricle, measured 1 cm. in its greatest diameter, and was composed of a firm, gray thrombus attached to an underlying cluster of tiny (1 mm.) elevations; the second, almost the same size, was located on the aortic leaflet of the mitral area, and the third was smaller and was located on the other mitral leaflet, the latter two being covered by a soft red blood clot. The chordae tendineae of the mitral valve were slightly thickened. The aortic valve was not appreciably changed. Cultures of the heart's blood and vegetations yielded *Str. viridans*. Microscopically, sections of the myocardium showed several moderately large areas in which the muscle fibers were replaced by areas infiltrated with lymphocytes and macrophages. The vegetations consisted mainly of fibroblasts with an interstitial infiltration of lymphocytes and macrophages, many of the latter being swollen or joined together to form giant cells. The outer edge of each vegetation was irregular and covered by masses of fibrin, erythrocytes and a few macrophages. An occasional cluster of gram-positive coccus-like bodies was found in the Gram-Weigert stained sections. No polymorphonuclear cells were present either in the vegetations or in the overlying blood clot.

The spleen weighed 220 Gm. and had three typical gray and moderately firm infarcts, one about 3.5 cm. and the other two about 1 cm. in greatest dimension. Histologically, these were large areas of infarct necrosis with surrounding zones of granulation tissue. On the capsular and cut surfaces of each renal cortex there were scattered red punctate lesions, but there were no gross infarcts. On microscopic examination an occasional glomerulus was found with a well formed crescent. There were interstitial collections of lymphocytes and plasma cells, and one subcapsular area contained engorged capillaries, extravasated blood and lymphocytic infiltration. No polymorphonuclear leukocytes were seen in any of the sections. There were a few petechiae along the gastrointestinal tract. In the lungs, the alveolar walls were congested. There were also lymphocytes and plasma cells and a few macrophages but no polymorphonuclear leukocytes either in the alveolar walls or within their lumens.

The femoral and vertebral bone marrow was grayish red and soft. Microscopically, the vertebral marrow showed an absence of maturation of the white blood cells. There was a moderately increased number of stem cells but only a few myelocytes and no adult polymorphonuclear neutrophils or eosinophils. Megakaryocytes were abundant, and the cells of the erythrocyte series were present in normal numbers. The femoral marrow was hyperplastic, but arrest of maturation of the white blood cells was present there also. There were

many stem cells, a few myelocytes, several megakaryocytes and areas of erythrocyte production but no adult polymorphonuclear cells.

The anatomic diagnoses were acute agranulocytosis; bacterial endocarditis involving the left auricular endocardium and mitral valve (*Str. viridans*); old rheumatic endocarditis of the mitral valve; splenic infarct, organizing; focal embolic glomerulonephritis and focal interstitial nephritis; pulmonary congestion (moderate), and petechial hemorrhages of the skin and gastrointestinal tract.

#### COMMENT

The clinical and pathologic pictures are characteristic of subacute bacterial endocarditis and acute agranulocytosis. The latter apparently began during the end of the third week of treatment with sulfathiazole. No other drugs known to produce this condition were used after treatment with sulfathiazole was begun, although sulfapyridine had been given for two days previously. No past history of treatment with sulfonamide drugs could be elicited. The exact cause or mechanism of the sudden death in this case is not certain. The appearance of the characteristic though mild rash, followed shortly by high fever and complete absence of granulocytes and a marked drop in the other leukocytic elements of the peripheral blood, leaves little doubt that we were dealing with acute agranulocytosis resulting from sulfathiazole therapy and that this was the determining factor in the fatal outcome.

In the present case, death from the underlying endocarditis was inevitable, but it might have been postponed had the leukopenia been recognized earlier and chemotherapy been stopped promptly thereafter. The events in this case serve to emphasize the importance of close observation of the blood in patients who are under prolonged therapy with sulfonamides. New related chemicals may be used in large numbers of cases before such serious complications are encountered. The early favorable experiences may result in excessive confidence and, in turn, in a relaxation of necessary and persistent care.

#### RECURRENT PNEUMOCOCCIC MENINGITIS TREATED WITH SULFAPYRIDINE

GEORGE B. CRADDOCK, M.D., AND RUSSELL V. BOWERS, M.Sc.  
RICHMOND, VA.

In 1938 Whitby<sup>1</sup> demonstrated the effectiveness of sulfapyridine against pneumococcic infections in mice. A number of favorable reports<sup>2</sup> have appeared which indicate that this drug has pronounced therapeutic value in the treatment of pneumococcic meningitis. During the past months Hodes and his associates<sup>3</sup> have used sulfapyridine and its sodium salt in 17 cases, with 47 per cent recovery. Recently Kolmer<sup>4</sup> presented a comprehensive review of sulfapyridine therapy in pneumococcic meningitis and discussed its therapeutic value.

We are presenting a patient with recurrent pneumococcic meningitis who was treated with sulfapyridine in each episode. The sulfapyridine concentrations of the blood and spinal fluid were of peculiar significance.

From the Departments of Medicine and Biochemistry, Medical College of Virginia.

1. Whitby, L. E. H.: *Chemotherapy of Pneumococcal and Other Infections*, Lancet 1: 1210 (May 28) 1938.

2. These reports include:

Reid, G. C. K., and Dyke, S. C.: *Pneumococcal Meningitis Treated with M. & B. 693*; Recovery, Lancet 2: 619 (Sept. 10) 1938.

Robertson, Kenneth: *Case of Pneumococcal Meningitis Treated with M. & B. 693*, ibid. 2: 728 (Sept. 24) 1938.

McAlpine, Douglas and Thomas, G. C.: *Pneumococcal Meningitis Treated with M. & B. 693*, ibid. 1: 754 (April 1) 1939.

MacKeith, R. C., and Oppenheimer, G.: *Pneumococcal Meningitis: Report of Five Consecutive Cases Treated with Sulfanilamide-Pyridine (M. & B. 693)*, ibid. 1: 1099 (May 13) 1939.

May, Kenneth: *A Fatal Case of Pneumococcal Meningitis Treated with M. & B. 693*, ibid. 1: 1100 (May 13) 1939.

Raman, P. S.: *Pneumococcal Meningitis Treated with M. & B. 693*, ibid. 1: 1101 (May 13) 1939.

Backhouse, T. C., cited by Ross, R. W.: *Acquired Tolerance of Pneumococcus to M. & B. 693*, ibid. 1: 1207 (May 27) 1939.

Barnett, H. L.; Hartmann, A. F.; Perley, A. M., and Ruhoff, M. B.: *The Treatment of Pneumococcal Infections in Infants and Children with Sulfapyridine*, J. A. M. A. 112: 518 (Feb. 11) 1939.

Cunningham, H. L.; Gimbel, H. S., and Burnett, G. W.: *Treatment of Pneumococcal Meningitis with Sulfapyridine*, J. A. M. A. 113: 1614 (Oct. 28) 1939.

3. Hodes, J. A.: *Progress in Chemotherapy of Bacterial and Other Diseases with Special Reference to the Protosis Sulfanilamide and Sulfapyridine*, Arch. Int. Med. 65: 671 (April) 1940.

4. Kolmer, J. A.: *Progress in Chemotherapy of Bacterial and Other Diseases with Special Reference to the Protosis Sulfanilamide and Sulfapyridine*, Arch. Int. Med. 65: 671 (April) 1940.

2. Autopsy was performed by Drs. J. B. Hamblet and P. C. Kennedy and the findings reviewed by Dr. Frederic Parker Jr.

## REPORT OF CASE

*First Admission.*—L. R., a Negro woman aged 32, was admitted to St. Philip Hospital (Negro division of the Medical College of Virginia hospitals) Dec. 15, 1939 and discharged apparently well December 31. Her history revealed that she had been well until the day before admission, when malaise and a severe frontal headache developed. She vomited once and later that night became irrational and stuporous.

Examination on admission revealed that the patient was obese and was in a disoriented condition; she could be aroused sufficiently to complain of a severe headache. There was marked nuchal rigidity. The blood pressure was 115 systolic and 50 diastolic. The heart was normal except for an insignificant apical systolic murmur and an occasional ectopic beat. Otherwise physical examination was negative except that the Kernig sign was present on both sides.

The urine had a specific gravity of 1.013, with albumin (2 plus), but showed no sugar or sediment. The temperature was 102 F., the pulse rate 80 and the respiratory rate 28. The blood showed hemoglobin 68 per cent, erythrocytes 3,870,000 and leukocytes 25,100 with 89 per cent polymorphonuclear neutrophils. The blood sugar level was 102 mg. per hundred cubic centimeters and the nonprotein nitrogen level 29 mg. per hundred cubic centimeters. The Kline test gave negative results. The spinal fluid pressure was 250 mm. of water. The fluid was cloudy and contained 8,000 cells per cubic millimeter, with 98 per cent polymorphonuclear neutrophils; pneumococcus type XVII was isolated from the spinal fluid.

The patient was first treated with sulfanilamide; an initial dose of 60 grains (4 Gm.) was given followed by 20 grains (1.3 Gm.) every four hours. Sulfanilamide was used until the causative organism was identified and then sulfapyridine in therapeutic doses was substituted. The drug was continued from December 16 to 27; clinical improvement with a normal temperature resulted on December 18.

The spinal fluid was normal on December 20 and the white blood cell count was 7,750. Sulfapyridine values of the blood and spinal fluid are given in the accompanying table.

*Second Admission.*—The patient was readmitted Jan. 24, 1940 and discharged apparently well Feb. 24. Her history in the interval was that she had been well after her discharge from the hospital until two days before readmission. At this time, January 22, she suffered headache, pain and stiffness of the neck. On the morning of admission her headache became severe; she had a chill and vomited.

The patient was rational; examination showed marked nuchal rigidity and the presence of Kernig's and Brudzinski's sign. The temperature was 103 F., pulse rate 120 and respiratory rate 26. The rest of the examination was not significant.

The urine was normal. The blood showed hemoglobin 68 per cent, erythrocytes 3,180,000 and leukocytes 11,700 with 79 per cent polymorphonuclear neutrophils. The spinal fluid was cloudy and the smear and culture were sterile.

The patient was treated with 60 grains (4 Gm.) of sulfapyridine on admission and 15 grains (1 Gm.) every four hours day and night from January 24 to February 1, then 15 grains every six hours until February 18 and then 7½ grains (0.5 Gm.) every six hours until her discharge from the hospital. Her temperature fell to normal twenty-four hours after sulfapyridine administration had been begun and remained so during her stay at the hospital. Because of lack of cooperation of the patient we were able to obtain only the one sample of spinal fluid. Examination, including roentgenograms, of the mastoids and paranasal sinuses, was negative for any focus of infection. She was discharged symptom free February 24 and did not report to the clinic as directed.

*Third Admission.*—She was readmitted for the third time on June 2 and discharged June 17, apparently recovered. The intervening history was that she had been well until the day before admission, at which time she awoke with a severe headache and vomited once. Later she became irrational and had a severe chill. Then she became stuporous and remained in this condition until she was readmitted.

On examination the patient was well developed and well nourished but was stuporous, with marked nuchal rigidity. Both the heart and the lungs were normal. Kernig's sign was present on both sides.

The urine was normal, and the blood studies showed 84 per cent hemoglobin, 4,160,000 erythrocytes and 23,900 leukocytes, with 85 per cent polymorphonuclear neutrophils. The spinal fluid was cloudy, and the pressure was 600 mm. of water; the leukocyte count was 45,000 with 82 per cent polymorphonuclear neutrophils. Pneumococcus type XXVIII was isolated from the spinal fluid.

Sulfapyridine was again administered in an initial dose of 60 grains and 15 grains every four hours. Recovery was prompt, and a normal temperature was present by June 5. Again the sulfapyridine levels of the blood and spinal fluid were determined; the blood level was 11.4 mg. and the spinal fluid level 26.2 mg. per hundred cubic centimeters on June 4.

*Fourth Admission.*—The patient was admitted for the fourth time October 16. Her history in the interval revealed that she had felt well and had continued working (at a tobacco factory) until the morning of this admission, when she suffered malaise, severe headache, aching over the body and pain and stiffness of the neck and back. She vomited several times; she also had a chill followed by fever. In the four month interval between her last discharge from the hospital in June and this admission she had noticed clear fluid dripping from her nose from time to time.

The patient was acutely ill, febrile and drowsy but could be aroused. She complained of headache and stiffness of the neck. There was no discharge from the nose. There was marked nuchal rigidity. Kernig's sign was absent. The remainder of

*Sulfapyridine Values of Blood and Spinal Fluid*

Date	Blood Level, Mg. per 100 Cc.	Spinal Fluid Level, Mg. per 100 Cc.
December 18	9.2	22.4
	12.3	48.0
	9.2	6.1
	8.0	1.0

the physical examination was negative except for diminished breath sounds and a few fine rales in the base of the left lung. The blood pressure was 110 systolic and 60 diastolic. The temperature was 104 F., the pulse rate 140 and the respiratory rate 40.

Lumbar puncture was performed; the fluid had a ground-glass appearance and was under a pressure of 250 mm. of water. Smear and culture of the spinal fluid failed to show the presence of any organism. The white cell count of the spinal fluid was 6,400 cells per cubic millimeter, with 80 per cent polymorphonuclear neutrophils. The protein content of the spinal fluid was over 100 mg. per hundred cubic centimeters.

Urinalysis was negative. The blood showed leukocytes 6,400 with 59 per cent polymorphonuclear neutrophils, erythrocytes 4,400,000 and hemoglobin 80 per cent. Blood sugar and non-protein nitrogen levels were normal.

Culture of the blood was negative for bacteria.

A roentgenogram taken with a portable apparatus confirmed the clinical diagnosis of bronchopneumonia in the lower lobe of the left lung. No sputum could be obtained. Culture of material from the nose showed no pneumococci.

The patient was treated with sulfapyridine as previously, 60 grains being given as the initial dose and 15 grains every four hours for six days and then 15 grains every six hours for eight more days, and then administration of the drug was discontinued. Her hemoglobin content and white blood cell count were observed during treatment, and neither showed a decrease.

The patient's clinical improvement was rapid. Her temperature fell to 100 F. in twenty-four hours and to normal in three days. It remained normal during the remainder of her stay in the hospital. Her spinal fluid cell count was 41 to the cubic millimeter, of which only 5 were polymorphonuclear neutrophils, on the fourth day.

Quantitative determinations of the sulfapyridine content of the blood and spinal fluid were made four days after the beginning of the administration of the drug. Unlike the values

obtained during the patient's first and third admissions, the blood sulfapyridine level was higher than the spinal fluid sulfapyridine level. The blood sulfapyridine level was 9.4 mg., and the spinal fluid sulfapyridine level was 7.1 mg. per hundred cubic centimeters.

Roentgen studies of the skull and paranasal sinuses failed to reveal any evidence of a basal fracture or of any abnormality of the sinuses or mastoids.

## COMMENT

We have presented a patient who has had suppurative meningitis four times within one year. On admission pneumococcus type XVII was isolated by culture from the spinal fluid. On the second admission the spinal fluid was sterile. On the third admission pneumococcus type XXVIII was isolated by culture from the spinal fluid and on the fourth admission the spinal fluid was again sterile. We cannot say whether the patient had four separate infections or whether the last three attacks were flare-ups from a dormant focus from the first infection. As far as we have been able to determine, there have been no cases of recurrent pneumococcal meningitis reported; this is probably due to the high mortality of this disease before the sulfapyridine era. Previous to the use of sulfapyridine, nearly all patients died before they could recover and suffer recurrences.

The recurrence of meningococcal meningitis is well known.<sup>5</sup> It may be due to infection of the paranasal sinuses or to small residual collections of pus within the meninges the breakdown of which causes a recurrence of the meningitis. Were it not for the fact that pneumococcus type XVII was isolated once, and later pneumococcus type XXVIII was isolated, we would feel that the "recurrence" was the result of encapsulated foci in the meninges. However, there is still a possibility of a transformation of the type of pneumococcus.

We regret that we could not study further the sulfapyridine levels of the spinal fluid, but each time the patient improved she fought any attempts at lumbar puncture, and we did not feel that it was safe to restrain her and perform the puncture under force.

The chemical examination of the blood and spinal fluid for free sulfapyridine according to Marshall's method<sup>6</sup> presented a rather interesting observation. In a previous case of pneumococcal meningitis we had demonstrated a blood value of less than one third of the spinal fluid value. This case led us to investigate like cases without a duplication of any such results, with the exception of the case just presented. During the past ten months we have analyzed the blood and spinal fluid of 8 patients and observed this in 2 of them.

Previously Cutts and his associates<sup>7</sup> reported the blood values higher in 1 case and Cunningham<sup>8</sup> made a similar observation in 1 case. Of the 17 patients of Hodes,<sup>3</sup> only 9 had comparable values, and in no case was the sulfapyridine concentration higher in the spinal fluid than in the blood. Our patient's spinal fluid values were higher than her blood values on her first and third admissions, but on her last admission her blood level was higher than the spinal fluid value. However, at the last admission the sulfapyridine concentration in the spinal fluid was 7.1 mg. per hundred cubic centimeters, which is above the usual level found in patients under treatment with the drug.

## SUMMARY

The patient here presented was admitted to the hospital four times within a year with suppurative meningitis. Twice a pneumococcus, each time of a different type, was isolated from the spinal fluid. The other times the spinal fluid showed no organisms on smear or culture. On each occasion sulfapyridine therapy was effectual.

On two admissions, the sulfapyridine concentration in the spinal fluid was greater than that in the blood. On the last admission the blood concentration was greater than the spinal fluid level.

## USE OF SULFATHIAZOLE IN STAPHYLOCOCCIC MENINGITIS WITH RECOVERY

JOSEPH F. SADUSK JR., M.D., AND AAGE E. NIELSEN, M.D.  
NEW HAVEN, CONN.

The seriousness of staphylococcal meningitis is well known, and only scattered reports of recovery from this condition, numbering less than a dozen, have appeared in the literature. The methods of treatment have consisted of simple cisternal drainage,<sup>1</sup> bacteriophage therapy,<sup>2</sup> administration of gentian violet,<sup>3</sup> sulfanilamide (or azosulfamide) therapy,<sup>4</sup> or combinations of these methods. Recently Dietel and Kaiser<sup>5</sup> made note of the recovery of a child with staphylococcal meningitis following therapy with sulfathiazole.

Sulfathiazole, synthesized by Fosbinder and Walter<sup>6</sup> and Lott and Bergeim<sup>7</sup> has attracted attention in the clinical treatment of staphylococcal infections<sup>8</sup> and its efficacy against the staphylococcus has been attested experimentally by *in vivo*<sup>9</sup> and *in vitro*<sup>10</sup> methods.

It has been recently shown<sup>11</sup> in this clinic, however, that sulfathiazole, unlike the other sulfonamide derivatives, does not readily diffuse into the noninflammatory cerebrospinal fluid. This finding immediately suggested the possible inefficacy of sulfathiazole in the treatment of meningeal infections and made evident the necessity for careful observation of the use of this drug in meningitis.

The present case is reported, first, to demonstrate that sulfathiazole does not readily diffuse into a purulent cerebrospinal fluid; second, to present evidence that an adequate concentration

The sulfathiazole used in this case was obtained through the courtesy of Dr. George A. Harrop, Squibb Institute for Medical Research, New Brunswick, N. J.

From the Departments of Internal Medicine and Surgery, Yale University School of Medicine, and the Medical and Surgical Services of the New Haven Hospital.

1. Jackson, R. L.: *Staphylococcus Aureus Meningitis: Report of Case with Recovery*, J. *Pediat.* **11**: 518 (Oct.) 1937.

2. Dunlap, J. E.: *Staphylococcal Meningitis with Recovery*, J. A. M. A. **104**: 1594 (May 4) 1935. Schless, R. A.: *Staphylococcus Aureus Meningitis: Treatment with Specific Bacteriophage*, Am. J. Dis. Child. **44**: 813 (Oct.) 1932. Stout, B. F.: *Septic Cavernous Sinus Thrombosis: Report of Two Cases with Recovery of One Following Bacteriophage Therapy*, J. Lab. & Clin. Med. **17**: 28 (Oct.) 1931; *Bacteriophage Therapy*, Texas State J. Med. **29**: 205 (July) 1933.

3. Bliss, R. L., and Hermann, E.: *Staphylococcal Septicemia with Meningitis and Multiple Abscesses Treated with Gentian Violet Intravenously: A Case Report*, J. Med. **17**: 247 (July) 1936. Lamb, F. H.: *Report of a Case of Staphylococcal Meningitis Treated with Intraventricular Injections of Gentian Violet*, Arch. *Pediat.* **45**: 306 (May) 1928.

4. Bloch, Harry, and Pacella, B. L.: *Staphylococcal Meningitis: Report of a Case in a Seventeen Day Old Infant Successfully Treated with Sulfanilamide*, J. A. M. A. **110**: 508 (Feb. 12) 1938. Findlay, H. V., and Hammel, M.: *Staphylococcus Aureus Meningitis: Report of a Case: Treatment with Sulfanilamide; Recovery*, California & West. Med. **51**: 324 (Nov.) 1939. Fritz, Milo, and Hollister, William: *Meningitis Due to Staphylococcus Aureus Haemolyticus: Report of a Recovery*, Arch. *Otolaryng.* **27**: 317 (March) 1938. Michels, M. W., and Gorme, W. S.: *Meningitis Due to Staphylococcus Aureus Haemolyticus Treated with Sulfanilamide*, Am. J. Dis. Child. **57**: 1379 (June) 1939. Pewterbaugh, D. C.: *Staphylococcus Aureus Meningitis: Report of Case*, Arch. *Pediat.* **56**: 623 (Oct.) 1939.

5. Dietel, F. W., and Kaiser, A. D.: *Staphylococcus Aureus Meningitis Successfully Treated with Sulfathiazole*, J. A. M. A. **115**: 601 (Aug. 24) 1940.

6. Fosbinder, R. J., and Walter, L. A.: *Sulfanilamide Derivatives of Heterocyclic Amines*, J. Am. Chem. Soc. **61**: 2032 (Aug.) 1939.

7. Lott, W. A., and Bergeim, F. H.: *2-(p-Aminobenzene)sulfonamide*—Thiazole: A New Chemotherapeutic Agent, J. Am. Chem. Soc. **61**: 3593 (Dec.) 1939.

8. Fitch, T. S. P.: *Sulfathiazole in Staphylococcus Aureus Epidural Abscess with Septicemia and Pyemia*, Arch. *Pediat.* **57**: 119 (Feb.) 1940. Stirling, W. C.: *Sulfathiazole: Two Cases of Septicemia with Recovery*, J. A. M. A. **115**: 118 (July 13) 1940.

9. Barlow, O. W., and Homburger, E.: *Specific Chemotherapy of Experimental Staphylococcus Infections with Thiazole Derivatives of Sulfanilamide*, Proc. Soc. Exper. Biol. & Med. **42**: 792 (Dec.) 1939. Bliss, Eleanor A., and Ott, E.: *Effect of Sulfapyridine, Sulfathiazole, and Sulfamethylthiazole upon Severe Staphylococcal Infection in Mice*, ibid. **43**: 706 (April) 1940. Long, P. H., and Bliss, Eleanor A.: *Bacteriostatic Effects of Sulfathiazole upon Various Microorganisms: Its Therapeutic Effects in Experimental Pneumococcal Infections*, ibid. **43**: 324 (Feb.) 1940. Rake, G., and McKee, C. M.: *Action of Sulfathiazole and Sulfamethylthiazole on Staphylococcus Aureus*, ibid. **43**: 561 (March) 1940.

10. Lawrence, C. A.: *Bacteriostatic Actions of Three Thiazole Derivatives of Sulfanilamide upon Bacteria in Broth Cultures*, Proc. Soc. Exper. Biol. & Med. **43**: 92 (Jan.) 1940. Long, P. H., and Bliss, Eleanor A.: *Bacteriostatic Effects of Sulfathiazole upon Various Microorganisms: Its Therapeutic Effects in Experimental Pneumococcal Infections*, ibid. **43**: 324 (Feb.) 1940. Rake, Geoffrey, and McKee, Clara M.: *Action of Sulfathiazole and Sulfamethylthiazole on Staphylococcus Aureus*, ibid. **43**: 561 (March) 1940.

11. Sadusk, J. F., Blake, F. G., and Seymour, A.: *Observations on the Absorption, Excretion, Diffusion, and Acetylation of Sulfathiazole in Man*, Yale J. Biol. & Med. **12**: 681 (July) 1940.

5. Meakins, J. C.: *Practice of Medicine*, ed. 2, St. Louis, C. V. Mosby Company, 1938.

6. Marshall, E. K., and Litchfield, L. T., Jr.: *The Determination of Sulfanilamide*, Science **88**: 85 (July 22) 1938.

7. Cutts, Morgan; Gregory, K. K., and West, E. J.: *Pneumococcal Meningitis Treated Successfully with Sulfapyridine*, J. A. M. A. **112**: 1456 (April 15) 1939.

8. Cunningham, A. A.: *Pneumococcal Meningitis Treated with Sulfanilamide and M. & B. 693*, Lancet **2**: 1114 (Nov. 12) 1938.

of sulfathiazole in the spinal fluid can be maintained by the intrathecal administration of a 0.5 per cent solution of sodium sulfathiazole in saline solution, and, third, to record the recovery of a case of *Staphylococcus aureus* meningitis treated by oral, parenteral and intrathecal therapy with sulfathiazole. This recovery is the only one which has occurred in 11 cases of staphylococcic meningitis observed at the New Haven Hospital during the past twelve years, despite varied types of therapy.

## REPORT OF CASE

**History.**—M. B., a man aged 40, an Italian, was admitted to the Neurological Unit of the Surgical Service (under the direction of Dr. William J. German) of the New Haven Hospital, July 3, 1940, because of Jacksonian convulsions on the left side. The history, physical examination and ventriculography demonstrated the presence of a space-occupying tumor in the right parietal region. On July 10 a right central craniotomy was performed by one of us (A. E. N.) with removal of a fibrillary astrocytoma situated in the right precentral leg area. Ventricular fluid removed at this time was crystal clear and contained 22.5 mg. of protein per hundred cubic centimeters.

The immediate postoperative course was moderately febrile, but the temperature approached normal limits by July 14. On July 16 a small amount of bloody fluid was aspirated from under the incision in the scalp. Because of increasing restlessness, lumbar puncture was done July 17 and 20 cc. of a crystal clear fluid under 260 mm. of water pressure was removed, apparently affording some degree of relief. Culture taken of this fluid remained sterile. On the following day (July 18) the patient complained of headache and a slightly stiff neck. The Kernig sign was equivocally present. There was a small amount of blood-tinged fluid draining from the craniotomy wound which on culture yielded a heavy growth of hemolytic *Staphylococcus aureus*. The temperature reached 102.8 F. that night and the patient became drowsy.

On the following day (July 19) the patient was irrational and semicomatose and signs of meningitis were definite, with stiff neck and the Kernig sign present bilaterally. The temperature was 104.2 F. A creamy, purulent, light red pus oozed copiously from the craniotomy wound. Lumbar puncture revealed the presence of cloudy cerebrospinal fluid under a pressure of 300 mm. of water. Smear of this fluid revealed the presence of gram-positive cocci, and on culture a moderate growth of hemolytic *Staphylococcus aureus* was obtained. Treatment with sulfathiazole was instituted the same afternoon, the patient receiving an initial dose of 4 Gm. by mouth, followed by 2 Gm. every four hours thereafter. On July 20 free drainage of the craniotomy wound was instituted by spreading the incision apart with a clamp and inserting two drains.

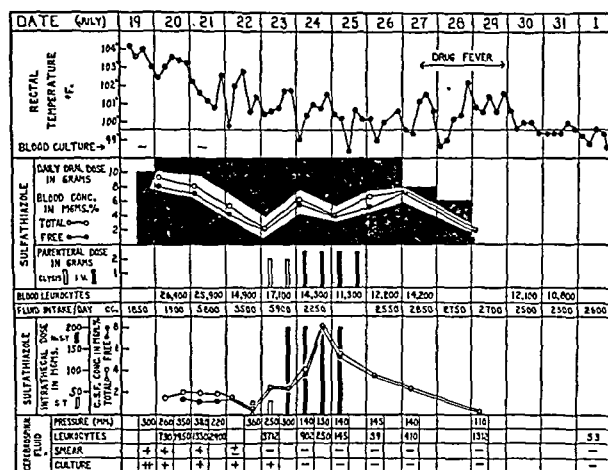
No definite improvement was noted during the next seventy-two hours, although drainage from the wound decreased and the patient appeared, perhaps, to be somewhat more conscious. On the other hand, the stiffness of the neck increased, both smear and culture of the spinal fluid remained positive for staphylococci, and the cellular elements of the cerebrospinal fluid, 95 per cent of which were polymorphonuclear leukocytes, steadily rose.

Since the sulfathiazole concentration<sup>12</sup> in the spinal fluid remained low in spite of an adequate concentration in the blood, it was thought advisable to begin intrathecal therapy with the drug. Accordingly, 30 cc. of a 0.1 per cent solution of sulfathiazole in physiologic solution of sodium chloride was administered intrathecally on July 22 and 23 following the drainage of 35 cc. of spinal fluid each time. Despite this procedure, the culture remained positive and the drug concentration rose but slightly. Hence, beginning July 23, the intrathecal administration of 40 cc. of 0.5 per cent sodium sulfathiazole in physiologic solution of sodium chloride was carried out twice a day in a manner similar to that already described. This procedure was sufficient to raise the sulfathiazole concentration in the cerebrospinal fluid to therapeutically satisfactory levels as demonstrated in the accompanying chart.

Coincident with these events, the sulfathiazole concentration in the blood steadily dropped to a low level of 2.2 mg. per

hundred cubic centimeters, despite the continued daily oral administration of 12 Gm. of sulfathiazole, perhaps in part because of the high fluid intake. An attempt was made to raise the blood concentration of the drug by the subcutaneous administration of 2 Gm. of sulfathiazole twice a day in addition to the ingestion by mouth of 12 Gm. of the drug. However, this form of parenteral therapy was not satisfactory because of the inordinately large quantities of saline solution required when the drug is administered by hypodermoclysis. The problem of maintaining therapeutically satisfactory blood concentration of sulfathiazole was eventually solved by the injection intravenously of a 1 per cent solution of the sodium salt of the drug in physiologic solution of sodium chloride, the precautions recommended by Marshall and Long<sup>13</sup> being observed. In addition to this, the patient continued to receive 12 Gm. of sulfathiazole a day by mouth.

Improvement following the intrathecal and intravenous administration of the sodium salt of the drug was striking. The patient became rational and alert, stiffness of the neck steadily decreased, and drainage of the craniotomy wound practically ceased. Return of function to the left side of the body was rapid, and the temperature continued to fall by lysis. In addition, the leukocyte count in both blood and cerebrospinal fluid dropped toward normal and culture of the cerebro-



Laboratory data of patient with staphylococcic meningitis treated with sulfathiazole: *clavis*, sulfathiazole given by hypodermoclysis; *I. V.*, sodium sulfathiazole administered intravenously; *NaST*, sodium sulfathiazole; *S. T.*, sulfathiazole; and *C. S. F.*, cerebrospinal fluid.

spinal fluid became sterile and remained so after the first intrathecal administration of sodium sulfathiazole. Details of these findings are given in the chart.

On the ninth day of sulfathiazole therapy the temperature began to rise, reaching 102 F. on July 28. Though no cutaneous eruption appeared, the most likely explanation of this fever appeared to be that of "drug fever." Consequently sulfathiazole was discontinued, with a resultant drop of the temperature to normal.

Improvement continued at a steady pace; the patient remained afebrile and was discharged from the hospital in good condition on August 10.

The rise of the leukocyte count in the cerebrospinal fluid to 410 per cubic millimeter on July 27 and to 1,312 on July 29 was due to the presence of large numbers of swollen and degenerated polymorphonuclear cells. In a final lumbar puncture, done on August 1, the spinal fluid was clear and contained 53 cells per cubic millimeter, all of which were mononuclear cells.

**Bacteriology.**—The organism isolated from the cerebrospinal fluid was a small gram-positive coccus occurring in smear in small clumps and growing on agar in small, glistening, convex colonies containing a faint golden pigment. On defibrinated rabbit's blood agar plates, both in pour and in streaked plates,

12. The chemical analyses in this report were performed by Miss Janet M. Grubb.

13. Marshall, E. K., and Long, P. H.: Intravenous Use of Sodium Sulfapyridine. *J. A. M. A.* 112:1671 (April 29) 1939.

the colony was surrounded by a small zone (1 mm.) of complete hemolysis. The latter in turn was surrounded by a band of incomplete hemolysis ranging from 1 to 3 mm. in width, depending on the size of the colony and its position with respect to the surface of the agar. Mannite, lactose, dextrose, sucrose and maltose were fermented with the production only of acid. The coagulase test gave positive results.

## COMMENT

Comment has previously been made on the failure of sulfathiazole to diffuse into noninflammatory spinal fluid in satisfactory concentration, as contrasted with the ready diffusion of sulfanilamide and sulfapyridine. That this failure is true also to a certain degree in the case of purulent fluids has recently been demonstrated by Spink and Hansen<sup>14</sup> in cases of pneumococcal meningitis. The present case confirms their observations.

The reason for this difference in diffusion into the cerebrospinal fluid between sulfathiazole and other compounds of the sulfonamide series is not clear at the present time. It should be pointed out that the finding of an unduly high concentration in the spinal fluid of any of the sulfonamide drugs should be interpreted with caution if procaine hydrochloride has been used, for, as Long and Wood<sup>15</sup> have pointed out, contamination of the fluid by procaine hydrochloride yields erroneously high results by virtue of the fact that the free amino groups in procaine hydrochloride combine with the coupling reagent to give an intense violet color. Therefore certain precautions must be taken in securing samples of spinal fluid as well as other types of body fluid for chemical analysis. In this clinic we have ordinarily preferred to dispense with procaine hydrochloride and use an ethyl chloride spray.

As soon as the inadequate diffusion of sulfathiazole into the cerebrospinal fluid in this case was known, it became evident that the oral use of this drug alone might not be satisfactory in the treatment of the meningitis. To date, no clinical report except that of Dietel and Kaiser<sup>5</sup> has appeared to confirm or contradict this possibility. Spink and Hansen<sup>14</sup> have treated three patients with pneumococcal meningitis with sulfathiazole but their report does not allow evaluation of the effect of sulfathiazole alone, since antiserum was used both parenterally and intrathecally.

That the use intrathecally of a 0.1 per cent solution of sulfathiazole in saline solution, which is about the limit of solubility of this drug at room temperature, may not be satisfactory, at least in staphylococcal meningitis, is apparent if one may judge from the absence of the obvious therapeutic effect in the present case. It is well known that more concentrated solutions of sulfathiazole may readily be made by the use of its sodium salt, but the high alkalinity of the 5 per cent solution commonly used for intravenous treatment might be expected to have a deleterious effect on the spinal cord. However, in view of the well-nigh fatal prognosis in cases of staphylococcal meningitis, we believed that the use of a 0.5 per cent solution of sodium sulfathiazole in saline solution should be tried as a last resort, after persistence of positive spinal fluid cultures and an increase in the symptoms of meningitis had occurred. The subsequent clinical improvement and disappearance of staphylococci from cultures of the spinal fluid would appear to have warranted the trial and speaks for the efficacy of this method of therapy.

Although this patient shows to date (Oct. 15, 1940) no evidence of damage to the central or peripheral nervous system that can be attributed to the drug, the possibility of injury to the spinal cord, even by a 0.5 per cent solution of sodium sulfathiazole, cannot be dismissed. Consequently, a further investigation of this problem is being undertaken.

The fact that on the same daily dosage there may be considerable variation in the blood concentration of sulfathiazole from patient to patient has been demonstrated.<sup>11</sup> The present case illustrates the fact that there may be a similar variation from day to day in the same patient and emphasizes the need

for daily determinations of the blood concentration of sulfathiazole in critically ill patients, with immediate resort to parenteral treatments if adequate blood concentration is not maintained by oral therapy alone. The administration of sulfathiazole by hypodermoclysis is ordinarily unsatisfactory, since the low solubility of the drug at room temperature necessitates the administration of excessively large quantities of saline solution. Therefore it may, under certain circumstances, be preferable to employ solutions of the sodium salt intravenously. Ordinarily a 5 per cent solution of sodium sulfathiazole in sterile distilled water is given intravenously, following the directions of Marshall and Long<sup>12</sup> in preparation of the solution. At times, to fortify oral therapy, we have used a 1 per cent solution of sodium sulfathiazole in physiologic solution of sodium chloride given intravenously, and this proved adequate in the case reported here.

## SUMMARY

1. In the case of *Staphylococcus aureus* meningitis reported, recovery occurred following sulfathiazole therapy.
2. Despite an adequate concentration in the blood, diffusion of sulfathiazole into the cerebrospinal fluid was unsatisfactory.
3. It was necessary to use a 0.5 per cent solution of sodium sulfathiazole intrathecally before sterilization of the spinal fluid was obtained. No ill effect from this solution could be demonstrated.
4. In order to maintain the blood concentration of sulfathiazole at a satisfactory level, the use of the sodium salt of the drug intravenously was necessary, despite dosage of 12 Gm. a day by mouth.

## RENAL COMPLICATIONS DUE TO SULFATHIAZOLE

CURTIS F. GARVIN, M.D., CLEVELAND

Urinary complications due to sulfathiazole have been described in animals<sup>1</sup> and in man.<sup>2</sup> At the Cleveland City Hospital, of fifty-four patients with pneumonia treated with sulfathiazole,<sup>3</sup> thirty-three (61.1 per cent) had crystals of the drug in the urine. In a control series of fifty-six patients treated with sulfapyridine, sixteen (28.6 per cent) had crystals in the urine. This difference is statistically highly significant.<sup>4</sup>

Sulfathiazole crystals appear in the urine more often than sulfapyridine probably because sulfathiazole is excreted more rapidly and hence a greater amount of the drug has to be administered in order to maintain a satisfactory concentration in the blood. In the cases under consideration an average dose of 52.4 Gm. of sulfathiazole administered over an average period

From the Department of Medicine of the Cleveland City Hospital and the Western Reserve University School of Medicine.

1. The experiments on animals include:  
Van Dyke, H. B.; Greep, R. O.; Rake, Geoffrey, and McKee, Clara M.: Observations on the Toxicology of Sulfathiazole and Sulfapyridine, *Proc. Soc. Exper. Biol. & Med.* **42**: 410 (Nov.) 1939.  
Cooper, F. B.; Gross, Paul, and Lewis, Marion: Chemotherapeutic Evaluation of Sulfanilamide Derivatives of Heterocyclic Amines, *Proc. Soc. Exper. Biol. & Med.* **42**: 421 (Nov.) 1939.  
Gross, Paul; Cooper, F. B., and Scott, R. E.: Urolithiasis Medicamentosa, *Urol. & Cutan. Rev.* **44**: 205 (April) 1940.  
Toomey, J. A.: Personal communication to the author.
2. The work on man includes:  
Reinhold, J. G.; Flippin, H. F., and Schwartz, Leon: Observations on the Pharmacology and Toxicology of Sulfathiazole in Man, *Am. J. M. Sc.* **199**: 393 (March) 1940.  
Long, P. H.: Thiazole Derivatives of Sulfanilamide, *J. A. M. A.* **114**: 870 (March 9) 1940.  
Flippin, H. F.; Schwartz, Leon, and Rose, S. B.: The Comparative Effectiveness and Toxicity of Sulfathiazole and Sulfapyridine in Pneumococcal Pneumonia, *Ann. Int. Med.* **13**: 2038 (May) 1940.  
Knoll, A. F., and Cooper, F. B.: Clinical Urolithiasis Medicamentosa Due to Sulfathiazole, *Urol. & Cutan. Rev.* **44**: 292 (May) 1940.  
Arnett, J. H.: Hematuria from Sulfathiazole Therapy in Pneumonia, *J. A. M. A.* **115**: 362 (Aug. 3) 1940.  
Pepper, D. S., and Horack, H. M.: Crystalline Concretions in the Renal Tubules Following Sulfathiazole Therapy: Widely Patent Foramen Ovale in a Patient Aged 77, *Am. J. M. Sc.* **199**: 674 (May) 1940.  
Long, P. H.; Haviland, J. W.; Edwards, Lydia B., and Bliss, Eleanor A.: The Toxic Manifestations of Sulfanilamide and Its Derivatives, *J. A. M. A.* **115**: 364 (Aug. 3) 1940.  
Allott, E. N.: Clinical Experiences with Sulfathiazole, *Brit. M. J.* **1**: 1033 (June 22) 1940.
3. Sulfathiazole was available for study through cooperation with the Squibb Institute for Medical Research and the Medical Research Division of the Winthrop Chemical Company.
4. In this article the term "significant" refers to a difference which could be produced by chance in less than 5 per cent of trials as demonstrated by application of the chi square test; "highly significant" refers to a difference so great that it could be produced by chance in less than 1 per cent of trials, again as demonstrated by application of the chi square test.

14. Spink, W. W., and Hansen, A. E.: Sulfathiazole: Clinical Evaluation, *J. A. M. A.* **115**: 840 (Sept. 7) 1940.

15. Long, P. H., and Wood, W. B.: Observations upon the Experimental and Clinical Use of Sulfapyridine. II. The Treatment of Pneumococcal Pneumonia with Sulfapyridine, *Arch. Int. Med.* **13**: 487 (Sept.) 1939.



of 5.2 days produced an average blood concentration of 5.8 mg. per hundred cubic centimeters of the free drug in the blood. In the cases treated with sulfapyridine, an average total dose of 34.4 Gm. given over an average period of 6.8 days resulted in an average blood concentration of 5.4 mg. per hundred cubic centimeters. In short, it took 10.1 Gm. of sulfathiazole a day in contrast to 5.1 Gm. of sulfapyridine to produce a blood level of from 5 to 6 mg. per hundred cubic centimeters.

Hematuria was found microscopically in eight cases in the sulfathiazole treated group (14.8 per cent) and in six in the sulfapyridine group (10.7 per cent), a difference which is not statistically significant. In most of the patients the hematuria was of no consequence. Two cases in the sulfathiazole treated group, however, were unusual:

## REPORT OF CASES

CASE 1.—A. D., a white man aged 65, entered the Cleveland City Hospital at 5:30 p. m. March 22, 1940, with type I pneumococcus pneumonia and received sulfathiazole. The dosage was 4 Gm. by mouth repeated in four hours, followed by 2 Gm. every four hours. The temperature became normal in thirty hours and improvement was definite.

On March 24, 25 and 26 the blood level of sulfathiazole was 6.8, 5.0, and 4.9 mg. per hundred cubic centimeters respectively. The urine, normal on March 23, showed crystals on the 24th and 25th and many crystals and a few red blood cells microscopically on the 26th. The administration of the drug was discontinued at once, a total of 48 Gm. having been given in three and one-half days.

Alkalis were administered, fluids were forced, and continuous hot compresses were applied to the renal regions. In the next twenty-four hours, despite an intake of 5,000 cc. by mouth and by vein, the patient voided only 200 cc. of urine, which on microscopic examination contained crystals of the drug and blood. The patient was sluggish and drowsy, and there was tenderness at both costovertebral angles. The blood urea nitrogen, which had been 24.2 mg. per hundred cubic centimeters on admission, was 56.7 mg. and the creatine 4.7 mg. At 3:30 p. m. March 28 he was catheterized and 75 cc. of urine was obtained. This contained no albumin but on microscopic examination from 10 to 20 red blood cells per high power field and many crystals of sulfathiazole were found. That evening the patient began to void increasingly large amounts of urine, and improvement was constant thereafter. The blood and crystals disappeared from the urine and the blood urea nitrogen fell to normal.

CASE 2.—L. S., a white man aged 55, entered the Cleveland City Hospital March 7, 1940, ill with type III pneumococcus pneumonia and received sulfathiazole. The initial dose was 4 Gm. followed by 2 Gm. every four hours for twenty-five doses and then 1 Gm. every four hours for twelve doses. The blood levels were 3.0, 4.5, and 1.9 mg. per hundred cubic centimeters on March 8, 11 and 12. The temperature was normal in sixty hours and clinical improvement was obvious.

From March 9 to 13, specimens of urine contained crystals of the drug. On March 13 from 5 to 10 red blood cells per high power field were also present and the patient complained of severe abdominal pain resembling renal colic. The use of the drug was stopped (56 Gm. had been given in five and one-half days). The patient was given 1.3 Gm. (20 grains) of potassium citrate every hour until the urine was alkaline. Fluids were forced.

The next day the patient had a dull aching pain in the left flank. Urinalysis gave about the same results. The following day only an occasional red blood cell could be found in the urine and the patient was better.

## SUMMARY

Thirty-three (61.1 per cent) of fifty-four patients with pneumonia treated with sulfathiazole showed crystals of the drug in the urine, in contrast to sixteen (28.6 per cent) of fifty-six patients treated with sulfapyridine. This is statistically a highly significant difference and probably is explained by the fact that 10.1 Gm. a day of sulfathiazole was required to produce a blood level of 5.8 mg. per hundred cubic centimeters, whereas 5.1 Gm.

of sulfapyridine was sufficient to result in a concentration of 5.4 mg. per hundred cubic centimeters.

The incidence of hematuria was 14.8 per cent for the sulfathiazole treated group and 10.7 per cent for sulfapyridine, a difference which is not statistically significant. One patient treated with sulfathiazole had crystals of the drug in the urinary tract which presumably caused hematuria, retention of nitrogenous products and oliguria of about thirty-six hours' duration. Another patient had hematuria and pain resembling renal colic, also presumably caused by crystals of sulfathiazole in the urine.

3395 Scranton Road.

## SPONTANEOUS MEDIASTINAL EMPHYSEMA

HAYES W. CALDWELL, M.D., BLUEFIELD, W. VA.

In recent years medical men's attention has been called to a syndrome that might aptly be called Hamman's syndrome, since he was the first to describe it.<sup>1</sup> He reported his observations in 1937 and more fully in 1939.<sup>2</sup> His cases had been seen over a period of five years. Scott<sup>3</sup> later in 1937 reported 2 cases with similar signs and symptoms. Since that time others have added to this series—Faulkner and Wagner<sup>4</sup> as well as Morey and Sosman.<sup>5</sup> Because of the importance of the subject I wish to add another case to those already published.

Hamman's explanation for the cause of this condition is that, owing to some weakness in an alveolar wall, it ruptures and the released air dissects its way through the fibrous tissue about the blood vessels into the hilus of the lung and thence into the mediastinal tissue. If the amount of escaped air is voluminous enough it is free to dissect further into the cervical tissues. Morey and Sosman<sup>5</sup> suggest that the frequent concomitant partial pneumothorax observed in some of these cases is due to air from a ruptured alveolus dissecting its way to the visceral pleura forming a pleural bleb which later ruptures. The latter assumption seems hardly necessary or justified. Such a pneumothorax might be produced by rupturing or diffusion from a mediastinal emphysematous bleb.

The onset of this condition is usually brought to the patient's attention with the sudden onset of substernal pain or discomfort, which is often referred to the back and shoulders, rarely to the arms. The age incidence in reported cases varies between 16 and 51 years. The duration of the pain varies from five or ten minutes to as many hours. Usually after about two hours or later the patient becomes conscious of a peculiar crackling noise emitting from his chest, coming with each heart beat. Often there is some associated discomfort and usually he discovers that changing positions might free him from this curious noise and discomfort, while lying on the left side usually intensifies or calls to his attention the aforementioned symptoms. Occasionally patients have leukocytosis and fever; rarely cyanosis and dyspnea are evident. There are no pathognomic electrocardiographic changes.

The finding of a peculiar crackling or bubbling sound heard over the precordium, usually best with the patient lying on his left side and occurring with each cardiac systole, first calls attention to the possibility of a mediastinal emphysema. As Hamman<sup>1</sup> states, the demonstration of subcutaneous emphysema in the cervical region or the finding of air in the mediastinum or pneumothorax by roentgen examination makes the diagnosis evident. However, the latter two findings are not always present.

The diagnosis of this condition is important in that other conditions with a more ominous prognosis, such as coronary occlusion, pericarditis, mediastinitis, ruptured aneurysm and

1. Hamman, Louis: Spontaneous Interstitial Emphysema of the Lung, *Tr. A. Am. Physicians* 52: 311, 1937.

2. Hamman, Louis: Spontaneous Mediastinal Emphysema, *Bull. Johns Hopkins Hosp.* 44: 1 (Jan.) 1939.

3. Scott, Agnes: Significance of Anginal Syndrome in Acute Spontaneous Pneumomediastinum, *Lancet* 1: 1327-1330 (June 5) 1937.

4. Faulkner, W. B., Jr., and Wagner, R. J.: Fatal Spontaneous Pneumothorax and Subcutaneous Emphysema in an Asthmatic, *J. Allergy* 8: 267-272 (March) 1937.

5. Morey, J. B., and Sosman, M. C.: Spontaneous Emphysema, *Radiology* 32: 19 (Jan.) 1939.

pulmonary embolus, may be forgotten once the diagnosis has been assured. The cases reported have required no treatment except some cases requiring medication for relief of pain.

My case will be reported briefly, as follows:

P. K., a well developed and nourished lawyer, walked into the Bluefield Sanitarium Hospital, Aug. 12, 1940, complaining chiefly of his heart thumping and of the associated clicking with each beat. His past history was noncontributory except possibly for a severe case of whooping cough at 12 years, which, he stated, nearly killed him. He had been feeling perfectly well until August 10, when he awakened about 3 a. m. with paroxysms of coughing that lasted off and on for two hours, interrupting his sleep. This was unusual for him. On awakening again about 8 o'clock he turned on his left side and became conscious of noisy thumping of his heart. He was able to work August 10, although this painful thumping and noise, which even his friends were easily able to hear, persisted. These queer sensations continued on the following day, but by then he was able to gain some relief by deep inspiration or stretching. Becoming very worried about himself, he came to the hospital along with his anxious family, insisting that he had severe heart trouble. A member of our medical staff jokingly reassured him and in turn was amazed when the man turned on his left side and, even while seated at his desk across the room, the physician was able to hear a loud rhythmic crunching noise. On examination the sounds were found to be synchronous with each heart beat.

On examination the patient, who was robust, was in no acute distress but rather apprehensive. He is an intelligent man. The blood pressure was 124 systolic and 74 diastolic, the pulse rate 80 and the temperature 99 F. There was no evidence of subcutaneous emphysema about his neck or shoulders and no evidence of pneumothorax. A percussion note was hyperresonant over the precordial area. The heart sounds were normal with the patient lying flat, but when he turned on the left side a loud clicking, crunching sound could be easily heard over the entire precordium which was almost painful to the ear. This sound was loud on expiration but disappeared entirely on deep inspiration. The noise was constantly present with each cardiac systole under the aforementioned conditions. At times, however, over the apical area a sound which might have been interpreted as a harsh diastolic murmur would come and go during expiration. The patient also demonstrated his ability to produce these former sounds by bending forward while standing. The physical examination was otherwise negative. A roentgen examination revealed the heart and great vessels to be normal, with no evidence of pneumothorax. The leukocyte count was 7,200. The sedimentation rate was 5 mm. in one hour. An electrocardiogram was normal.

Fortunately I had a copy of Dr. Hamman's report, and the diagnosis became obvious. The patient was more relieved after reading this reprint than with any assurance I could give him. After a week's time his complaints and signs had completely disappeared.

I convinced myself about the physical manifestations of mediastinal emphysema by finding about one month later crackling sounds over the precordial area of a patient admitted to the hospital after receiving a stab wound which pierced the mediastinal tissue just to the left of the sternum in the fourth intercostal space. The laceration was sutured, and the following morning crackling, bubbling sounds could be heard synchronous with each heart beat, loudest on forced expiration. The sounds had disappeared by the following afternoon. The patient experienced no discomfort.

#### CONCLUSION

1. The most consistent finding in mediastinal emphysema is a crunching, bubbling sound over the precordium synchronous with heart beats.
2. Confirmatory signs are subcutaneous emphysema about the cervical region and the roentgen finding of pneumothorax or evidence of emphysema around the heart or in the mediastinum.
3. Patients usually show few constitutional symptoms.
4. The diagnosis can easily be made if the possibility of mediastinal emphysema is kept in mind.

## Special Article

### GLANDULAR PHYSIOLOGY AND THERAPY

#### THE NEUROHYPOPHYSIS

E. M. K. GEILING, PH.D., M.D.

AND

FRANCES K. OLDHAM, PH.D.

CHICAGO

*This special article is published under the auspices of the Council on Pharmacy and Chemistry. It is one of a series which will be published in book form as the second edition of "Glandular Physiology and Therapy." The opinions expressed in this article are those of the author and do not necessarily represent the views of the Council.—Ed.*

The neurohypophysis consists of three poorly defined regions: (1) the neural lobe, (2) the infundibular stem and (3) the median eminence (or part thereof<sup>1</sup>). Because of the intimate contact of the neural and the intermediate lobe in man and most laboratory animals, these two parts of the pituitary gland are frequently classed together as the posterior lobe. However, with the clarification of the development and of the secretory capacity of the neural division of the hypophysis, it becomes expedient to abandon the use of a term based purely on gross anatomic relations.

The primary structural elements of the neurohypophysis are pituicytes and unmyelinated nerve fibers. The pituicytes are derived from the ependymal cells of the neural tube and are closely related to neuroglia. They have one or more cytoplasmic processes, and frequently these end in close relation to blood vessels or connective tissue.<sup>2</sup> The nerve fibers have their cells of origin in the supraoptic and tuberous nuclei. They sweep down the infundibular stem in dense bundles and spread out in the neural lobe, forming a rich network about the cells.<sup>3</sup>

#### ORIGIN AND PATH OF ESCAPE OF THE SECRETION

It was formerly believed that the so-called "posterior lobe hormones" (pressor, antidiuretic, oxytocic and melanophore-dispersing principles) were elaborated by the pars intermedia. Support for this view came from the close association between the neural and the intermediate lobe in most species and from the reluctance of many investigators to ascribe a secretory role to cells of nervous origin.<sup>4</sup> However, during the past five years, convincing evidence has been adduced to prove that the pressor, antidiuretic and oxytocic hormones arise from the intrinsic elements of the neurohypophysis. In studies of species in which a pars intermedia is lacking (the cetaceans, the armadillo, the chicken

From the Department of Pharmacology, University of Chicago.

1. Weaver, T. A., Jr., and Bucy, P. C.: The Anatomical Relationships of the Hypophyseal Stem and the Median Eminence, *Endocrinology* 27: 227 (Aug.) 1940.
2. Bucy, P. C.: The Pars Nervosa of the Bovine Hypophysis, *J. Comp. Neurol.* 50: 595 (Aug.) 1930. Griffiths, Mervyn: The Relationship Between the Secretory Cells of the Pars Nervosa of the Hypophysis and Classical Neuroglia, *Endocrinology* 26: 1032 (June) 1940.
3. Rasmussen, A. T.: Innervation of the Hypophysis, *Endocrinology* 23: 263 (Sept.) 1938.
4. Cushing, Harvey: Posterior Pituitary Activity from an Anatomical Standpoint, *Am. J. Path.* 9: 539 (Sept.) 1933.

and the South American manatee<sup>5</sup>) it has been shown that these three principles are present in extracts of the neural lobe, whereas the melanophore-dispersing factor is present only in extracts of the anterior lobe.<sup>6</sup> The colloid masses, or Hering bodies, frequently considered to be secretory antecedents migrating from the intermediate lobe into the neurohypophysis, are believed to be fixation artefacts.<sup>7</sup> Interruption of the nerve tracts to the neurohypophysis results in degenerative changes in the pituicytes and loss of pressor, antidiuretic and oxytocic activity.<sup>8</sup> Changes in the pituicytes have been correlated with secretory activity.<sup>9</sup> Tissue cultures of the neural lobe admixed with the intermediate lobe have pressor and melanophore-dispersing activity, while those of the intermediate lobe alone have only melanophore-dispersing activity.<sup>10</sup>

While the evidence points to the pituicytes as the secretory elements, the function of the nerve fibers is not as yet clear. There is evidence that a reflex connection exists between the vagus and the supraoptico-hypophysial tract.<sup>11</sup>

The neurohypophysis receives a fairly rich blood supply from the inferior hypophysial arteries. Its venous drainage is into the circular sinus.<sup>12</sup> Recent failures to detect the posterior lobe principles in cerebrospinal fluid do not support the view once advanced that these principles escape by way of the third ventricle.<sup>13</sup> Massive intravenous doses of pressor and oxytocic substances are excreted in part unchanged in the urine.<sup>14</sup> Efforts to demonstrate these factors in blood or urine under physiologic conditions have yielded contradictory results.<sup>15</sup>

#### CHEMISTRY OF EXTRACTS OF THE POSTERIOR LOBE

Although several commercial preparations of the posterior lobe of the hypophysis are available for clinical use, as yet none of the active principles have been isolated as chemically pure entities. Abel and his associates<sup>16</sup> have isolated a tartrate of high purity possessing pressor, oxytocic and antidiuretic properties. Kamm and co-workers<sup>17</sup> and more recently Stehle<sup>18</sup> and others have separated from pituitary extracts two fractions, pitressin and pitocin, which have been highly purified.

The treatment of posterior pituitary preparations with enzymes has given rise to results which are subject to different interpretations.<sup>19</sup> Gulland and his associates reported that an inactivating enzyme accompanies preparations of dipeptidase, aminopolypeptidase, trypsin and papain but that it is not identical with any of these. Larson confirmed the reports of earlier workers and expressed the opinion that the inactivation is due to the aminopeptidases of the tissue ereptases. He suggested that this enzymatic process may be one of the factors in the diminution of pressor response to successive doses of pituitary extract. Thus far, no enzyme acting in an acid range has been found that will destroy the active factors of the posterior lobe. Indubitably, other factors, besides enzymes, cause loss of activity, such as adsorption, hydrogen ion concentration, incubation time and temperature.<sup>20</sup>

Recent studies on electrophoresis indicate that both the pressor and the oxytocic principle are possibly amphoteric and are certainly basic in nature.<sup>21</sup> When such experiments are conducted in a medium below a certain  $p_H$  (the value of which differs in each report) the oxytocic substance migrates to the cathode. According to duVigneaud and his associates, the pressor substance migrates in the same direction at an even more rapid rate, since its concentration in the cathode vessel is greater than that of the oxytocic substance. Irving and duVigneaud repeated this experiment on the press juice from fresh glands with the same general result. This they advanced as evidence that the two principles exist as separate entities in the natural state.<sup>22</sup>

5. Valsø, Jacob: Der Hormongehalt der Hypophyse des Blauwals (*Balaenoptera sibbaldii*), Klin. Wehnschr. 13:1819 (Dec. 22) 1934. Geiling, E. M. K.: The Hypophysis Cerebri of the Finback (*Balaenoptera Physalis*) and Sperma (Phocaena), J. Comp. Path. & Therap., Bull. Johns Hopkins Hosp. 57:123 (Sept. 1938). Oldham, Frances K.: The Site of Secretion of the Posterior Pituitary Hormones, Tr. A. Am. Physicians 52:132, 1937. Oldham, Frances K.; McCleery, D. P., and Geiling, E. M. K.: A Note on the Histology and Pharmacology of the Hypophysis of the Manatee (*Trichechus Inunguis*), Anat. Rec. 71:27 (May 25) 1938. Oldham, Frances K.: The Pharmacology and Anatomy of the Hypophysis of the Armadillo, ibid. 72:265 (Nov. 25) 1938.

6. It is generally conceded that in those species possessing a discrete intermediate lobe, the melanophore-dispersing hormone is secreted by the cells thereof.

7. Gersh, Isidore, and Tarr, A. deL.: The So-Called Hyaline Bodies of Herring in the Posterior Lobe of the Hypophysis, Anat. Rec. 63:231 (Oct. 25) 1935.

8. Fisher, Charles, and Ingram, W. R.: The Effect of Interruption of the Supraoptico-Hypophysial Tracts on the Antidiuretic, Pressor and Oxytocic Activity of the Posterior Lobe of the Hypophysis, Endocrinology 20:762 (Nov.) 1936.

9. Gersh, Isidore: The Structure and Function of the Arachnoid Glandular Cells in the Neurohypophysis of the Rat, Am. J. Anat. 64:407 (May) 1939. Wang, Kun-jen: A Vagus Post-Pituitary Reflex: V. The Secretory Cells of the Pars Nervosa, Chinese J. Physiol. 13:405 (Dec.) 1938.

10. Geiling, E. M. K., and Lewis, M. R.: Further Information Concerning the Melanophore Hormone of the Hypophysis Cerebri, Am. J. Physiol. 113:534 (Nov.) 1935. Anderson, Evelyn, and Haymaker, Webb: Elaboration of Hormones by Pituitary Cells Growing in Vitro, Proc. Soc. Exper. Biol. & Med. 33:313 (Nov.) 1935.

11. Chang, H. C.: The Establishment of a Vagus-Post-Pituitary Reflex: A Review, Chinese M. J. 5:6:360 (Oct.) 1939. Sattler, D. G.: Vago-Neurohypophysial Pressor Reflex, Proc. Soc. Exper. Biol. & Med. 44:82 (May) 1940.

12. Wislocki, G. D.: The Vascular Supply of the Hypophysis Cerebri of the Rhesus Monkey and Man, Proc. A. Research Nerv. & Ment. Dis., Proc. (1936) 17:48, 1938.

13. Van Dyke, H. B.; Bailey, Percival, and Bucy, P. C.: The Oxytocic Substance of the Cerebrospinal Fluid, J. Pharmacol. & Exper. Therap. 36:595 (Aug.) 1929. Friedman, Gertrude S., and Friedman, M. H.: An Examination of Cerebrospinal Fluid for Oxytocic Activity as Tested by the Rabbit Uterine Fistula Preparation, Am. J. Physiol. 103:244 (Jan.) 1933. Simon, Alexander: The Secretion of the Posterior Lobe of the Hypophysis After the Administration of Drugs, J. Pharmacol. & Exper. Therap. 49:375 (Nov.) 1933.

14. Larson, Edward: Tolerance and Fate of the Pressor Principle of Posterior Pituitary Extract in Anesthetized Animals, J. Pharmacol. & Exper. Therap. 62:346 (March) 1938; Fate of the Injected Oxytocic Principle of Posterior Pituitary in Anesthetized Dogs, ibid. 67:175 (Oct.) 1939.

15. Gilman, Alfred, and Goodman, Louis: The Secretory Response of the Posterior Pituitary to the Need for Water Conservation, J. Physiol. 100:113 (July 15) 1937. Walker, A. M.: Experiments upon the Relations Between the Pituitary Gland and Water Diuresis, Am. J. Physiol. 127:541 (Oct.) 1939.

16. Abel, J. J.; Rouiller, C. A., and Geiling, E. M. K.: Further Investigations on the Oxytocic-Pressor-Diuretic Principle of the Infundibular Portion of the Pituitary Gland, J. Pharmacol. & Exper. Therap. 22:289 (Nov.) 1923.

17. Kamm, Oliver; Aldrich, T. B.; Grote, J. W.; Rowe, L. W., and Bugbee, E. P.: The Active Principles of the Posterior Lobe of the Pituitary Gland: I. The Demonstration of the Presence of Two Active Principles; II. The Separation of the Two Principles and Their Concentration in the Form of Potent Solid Preparations, J. Am. Chem. Soc. 50:573 (Feb.) 1928.

18. Stehle, R. L.: New Method for Separating Pressor and Oxytocic Substances from Posterior Lobe of Pituitary Gland, J. Biol. Chem. 102:573 (Oct.) 1933.

19. (a) Gulland, J. M., and MacRae, T. F.: The Oxytocic Hormone of the Posterior Pituitary: III. The Action of Plant Proteolytic Enzymes, Biochem. J. 27:1237, 1933; IV. The Action of Animal Proteolytic Enzymes, ibid. 27:1383, 1933. (b) Dale, H. H., and Dudley, H. W.: On the Pituitary Active Principles and Histamine, J. Pharmacol. & Exper. Therap. 18:27 (Aug.) 1921. (c) Thorpe, W. V.: Experiments on the Chemical Nature of the Oxytocic Principle in the Pituitary Gland, Biochem. J. 20:374, 1926. (d) Freudenberg, Karl; Weiss, Emil, and Biller, Hans: Notiz über Oxytocin, Ztschr. f. physiol. Chem. 233:172, 1935. (e) Heller, H., and Urban, F. F.: The Fate of the Antidiuretic Principle of Post Pituitary Extracts in Vivo and in Vitro, J. Physiol. 85:502, 1935. (f) Heller, H.: The State in the Blood and the Excretion in the Kidney of the Antidiuretic Principle of the Posterior Pituitary Extracts, ibid. 89:81 (Feb. 19) 1937.

20. Vaichulis, J. A.: The Effect on the Posterior Pituitary Principles of Incubating Beef Heads at Thirty-Seven Degrees Centigrade for Twenty-Four Hours, J. Pharmacol. & Exper. Therap. 63:37 (May) 1938. A Simple Method of Removing the Oxytocic Principle from the Posterior Lobe of the Beef Pituitary Glands, ibid. 66:37 (May) 1939.

21. Das, N.; Ghosh, B. N., and Guha, D. C.: Bemerkung zur Elektrodialyse von Oxytocin, Ztschr. f. physiol. Chem. 228:131, 1936. Gulland, J. M.; Lucas, N. S.; Freeman, M., and Randall, S. S.: The Oxytocic Principle of the Posterior Pituitary: Adsorption, and Electro-Adsorption Spectra, J. Biol. Chem. 122:208, 1935. du Vigneaud, Vincent, and Sealock, R. R.: Electrophoresis of Posterior Pituitary Extracts, J. Biol. Chem. 123:45 (March) 1938.

22. Irving, G. W., Jr., and du Vigneaud, Vincent: The Differential Migration of the Pressor and Oxytocic Hormones in Electrophoretic Studies of the Untreated Press Juice of the Posterior Lobe of the Pituitary Gland, J. Biol. Chem. 122:485 (April) 1938.

A preliminary study by Rosenfeld of sedimentation properties in the ultracentrifuge indicates that the pressor and oxytocic principles exist normally as relatively large molecules, which are broken down to smaller, physiologically active products by the usual methods of chemical extraction.<sup>23</sup>

Perhaps the most significant recent chemical finding has been the demonstration in three separate laboratories that the pressor and the oxytocic factor each possesses at least one reduction-oxidation system, presumably connected with the S-S group of cysteine.<sup>24</sup>

Analytic work by Stehle and others on highly purified preparations indicates a high amino acid content in both pressor and oxytocic principles. The amino acids found in largest amounts are cysteine, tyrosine and arginine.<sup>25</sup>

Many of the problems relating to the chemical and the physiologic actions of these substances must await final solution until the "mother substance" of Abel,<sup>26</sup> or the fractions derived therefrom or existing separately, are obtained as chemically pure compounds. These should be of astounding potency, judging from the high degree of physiologic activity exhibited by impure preparations.

At present there is available an international pituitary powder, against which all commercial preparations are standardized. The unit of pituitary potency is the activity contained in 0.5 mg. of the standard pituitary powder (U. S. P. XI).

#### PHYSIOLOGIC EFFECTS

Posterior pituitary extract (solution of posterior pituitary U. S. P. XI) exerts striking physiologic actions on the cardiovascular, respiratory and renal systems, on smooth muscle, on certain glandular structures and on the metabolism. The separation of pitressin and of pitocin from pituitary extracts necessitated apportioning these multiple pharmacodynamic actions. Pitressin elicits the cardiovascular, respiratory, renal, intestinal and certain metabolic effects, and pitocin the oxytocic action. Both substances cause hyperglycemia and act as antagonists to insulin. The mechanism of action of each in this respect is probably different, and the relative effectiveness depends on the species of animal used.<sup>27</sup>

#### CARDIOVASCULAR AND METABOLIC EFFECTS

In man, therapeutic doses of either solution of pituitary U. S. P. or of pitressin, given intramuscularly or subcutaneously, do not cause any significant rise of blood pressure, in spite of the marked pallor, which would lead one to infer that the arterial tension is

elevated.<sup>28</sup> There is a decided but brief fall in the pulse rate, oxygen consumption and cardiac output, which is followed by a more prolonged rise.<sup>29</sup> Pitocin causes only a slight increase in oxygen consumption and negligible changes in the circulation. The decreased cardiac output after the injection of solution of pituitary or of pitressin is due largely to coronary constriction, which may be obviated by the administration of epinephrine or ephedrine.<sup>30</sup> The subsequent elevation in cardiac output and pulse rate is due to the accumulation of catabolites during the period of decreased consumption of oxygen after the administration of these drugs. This accumulation of catabolites causes a condition of "oxygen debt," the liquidation of which is manifested in the later increase in oxygen consumption.

In trained unanesthetized dogs the effects of these drugs in larger doses per kilogram of body weight, given intravenously, are more intense but essentially similar to those found in man, except for the blood pressure.<sup>31</sup>

In experimental animals the blood pressure response to solution of pituitary and to pitressin is determined by several factors, such as dose, time between injections, type and depth of anesthesia and species of experimental subject. Small doses given to normal anesthetized dogs or cats cause peripheral vasoconstriction with a sharp rise of pressure. Repeated doses give a lessened response, and tolerance is easily acquired. Larger doses given to intact animals with or without anesthesia may cause a fall in pressure followed by a rise. The depressor effect is due to coronary constriction.<sup>30</sup> In experiments in which cardiac effects are eliminated by the use of the Gibbs artificial heart, large doses of solution of posterior pituitary or of pitressin invariably cause a sharp rise of pressure, and subsequent injections produce little or no effect. Such experiments indicate that the depressor action is cardiac and that the tolerance factor is vested in the peripheral structures. In the fowl, pitocin gives a fall in pressure. This is a quantitative reaction and has been adapted as a method of assay for the oxytocic principle.<sup>32</sup>

#### RESPIRATORY EFFECTS

The respiratory changes are secondary to the circulatory effects. In unanesthetized animals there is a quickening of the respiratory rate interspersed with periods of cessation of breathing.<sup>16</sup>

#### RENAL EFFECTS: DIURETIC-ANTIDIURETIC ACTION

While the antidiuretic action of posterior pituitary is generally associated with the pressor fraction, recent studies by Heller suggest that it may be due to a separate entity, since heat inactivation of the pressor principle proceeds at a faster rate than that of the anti-

23. Rosenfeld, Morris: The Native Hormones of the Posterior Pituitary Gland: The Pressor and Oxytocic Principles, *Bull. Johns Hopkins Hosp.* **66**: 398 (June) 1940.

24. Gulland, J. M., and Newton, S. S.: The Oxytocic Hormone of the Posterior Lobe of the Pituitary Gland: V. Recognition as an Oxidation-Reduction System, *Biochem. J.* **29**: 378, 1935. Sealock, R. R., and du Vigneaud, Vincent: Studies on the Reduction of Pitressin and Pitocin with Cysteine, *J. Pharmacol. & Exper. Therap.* **54**: 433 (Aug.) 1935.

25. Sealock, R. R., Sifferd, R. H., Kamm, J. C.: Some Chemical Properties of Highly Purified and Pitocin, *J. Biol. Chem.* **100**: xciv (May) 1935. Stehle, R. L., and Fraser, A. M.: The Purification of the Pressor and Oxytocic Hormones of the Pituitary Gland, *J. Biol. Chem.* **100**: 136 (Oct.) 1935. Stehle, R. L., and Trister, S.: Concerning the Chemistry of the Pressor and Oxytocic Hormones of the Pituitary Gland, *ibid.* **65**: 343 (April) 1939.

26. Abel, J. J.: On the Unitary versus the Multiple Hormone Theory of Posterior Pituitary Principles, *J. Pharmacol. & Exper. Therap.* **40**: 139 (Oct.) 1930.

27. Ellsworth, H. C.: The Antagonism Between Posterior Lobe Pituitary Hormones and Insulin, *J. Pharmacol. & Exper. Therap.* **56**: 417 (April) 1936. Holman, D. V., and Ellsworth, H. C.: The Hyperglycemic Constituent of Posterior Pituitary Extract, *ibid.* **55**: 377 (March) 1935. Ellsworth, H. C.: The Action of Posterior Pituitary Hormone upon the Blood Sugar of the Rabbit, *ibid.* **55**: 435 (Dec.) 1935.

28. Moffat, W. M.: The Effect of Pituitrin Injections on Blood Pressure in Man, *Am. J. M. Sc.* **186**: 854 (Dec.) 1933.

29. Grollman, Arthur, and Geiling, E. M. K.: The Cardiovascular and Metabolic Reactions of Man to the Intramuscular Injection of Posterior Pituitary Liquid (Pituitrin), Pitressin, and Pitocin, *J. Pharmacol. & Exper. Therap.* **46**: 447 (Dec.) 1932.

30. Melville, K. L., and Stehle, R. L.: The Antagonistic Action of Epinephrine (or Adrenalin) upon the Coronary Constriction Produced by Pituitary Extract and Its Effect upon Blood Pressure, *J. Pharmacol. & Exper. Therap.* **42**: 455 (Aug.) 1931. Melville, K. L.: The Electrographic and Blood Pressure Changes Induced by Posterior Pituitary Extract (Postlobin-V) and the Influence of Ephedrine Thereon, *ibid.* **64**: 86 (Sept.) 1938. The Action of Pituitary Extract on the Blood Pressure of the Normal Unanesthetized Animal and the Effect of Ephedrine or Adrenaline Thereon, *ibid.* **47**: 355 (March) 1933. Rose, J. B.; Dreyer, N. B., and Stehle, R. L.: The Cardiac Action of Pituitary Extract (Posterior Lobe), *ibid.* **38**: 461 (April) 1930.

31. Geiling, E. M. K., and DeLawder, A. M.: Metabolic Changes Following the Intravenous Injection of Posterior Pituitary Extracts and Their Correlation with the Well Known Pharmacodynamic Action of the Drugs, *Bull. Johns Hopkins Hosp.* **51**: 1 (July) 1932.

32. Coon, J. M.: A New Method for the Assay of Posterior Pituitary Extracts, *Arch. internat. de pharmacodyn. et de therap.* **62**: 79 (May 31) 1939.

diuretic principle.<sup>33</sup> Therapeutic doses of either solution of pituitary or pitressin cause a marked antidiuretic effect lasting some hours in patients with diabetes insipidus or in normal subjects who have previously ingested water by mouth. This action is apparently a renal effect due to increased reabsorption of water by certain cells of the tubule.<sup>34</sup> Extrarenal effects, such as changes in the blood electrolytes<sup>35</sup> or inhibition of some hypothetic water center in the hypothalamus,<sup>36</sup> are probably of only secondary importance in the diuresis-inhibiting action of posterior pituitary.

A diuretic effect is best elicited with anesthetized rabbits rendered diuretic by feeding of greens, by rapid intravenous infusion of isotonic sucrose or by administration of phlorhizin. Unanesthetized animals with low urine flow may also respond in this way. This diuresis may be due to increased glomerular filtration or to decreased reabsorption of water by the tubules. According to Heller, the diuretic effect is due to the pressor and not to the antidiuretic principle.<sup>37</sup>

#### ACTION ON THE GASTROINTESTINAL TRACT

Variations in species of animal, in technic and in the portion of the gastrointestinal tract used account for the lack of concordance in the results obtained by different workers with preparations of the posterior pituitary principles. In the unanesthetized dog pitressin stimulates intestinal activity and causes defecation, while the oxytocic substance has an antagonistic influence in respect to these actions.<sup>38</sup>

Massive doses of posterior pituitary preparations give rise to gastric ulcers, due probably to local ischemic action by the pressor principle.<sup>39</sup>

#### OXYTIC EFFECTS

A number of workers<sup>40</sup> by *in vitro* and *in vivo* experiments on the uterus have made it clear that the nature and the degree of the reaction of the uterine musculature to posterior lobe preparations depend on (a) the species of the animal, (b) the phase of the menstrual or estrous cycle, (c) whether the uterus is gravid or nongravid and (d) the stage of pregnancy—early or late, in parturition or in the puerperium. Some of the variations in the uterine response become more intelligible when viewed in the light of the newer researches dealing with the effect on the uterus of the

estrogenic and corpus luteum hormones and their interplay with the hormones from the anterior and posterior lobes of the pituitary. Briefly stated, the reaction of the uterine muscle to pituitary preparations is markedly affected by the nature of that ovarian, placental or anterior pituitary hormone whose influence is preponderant at the time of injection. During the early stages of pregnancy the human uterus does not react to pitocin, probably because of the inhibitory effect of the luteal secretion. It does, however, respond to small doses of pitressin; whether the response is due to an effect of the drug *per se* or to mechanical factors remains a moot point. Later in the gestation period the reactivity to pitocin returns, and during parturition the uterus is very reactive to this substance and also to solution of pituitary. It is at this time that these drugs are mainly used by obstetricians. The influence of estrogenic substances in rendering the uterus more highly reactive comes into play here. In the puerperium, however, while involution is in progress, pitocin evokes little or no response.

In respect to the nongravid human uterus, both *in vitro* and *in vivo* studies indicate that pitressin is more effective than pitocin in eliciting contractions. According to Knaus, the uterus is highly reactive to posterior pituitary preparations during the first half of the menstrual cycle, but during the second half the reactivity is low. He attributed these changes to the liberation of progesterone following ovulation, and he presented these findings as evidence in support of the Ogino-Knaus theory of periodic fertility in women. Certain other investigators have been unable to confirm Knaus's findings.

For a more detailed discussion of the problem, the recent work of Reynolds should be consulted.<sup>41</sup>

The excised horns of the virgin guinea pig's uterus are very reactive to solution of pituitary and to pitocin; this action forms the basis of the official method of assay of these drugs.

#### CLINICAL USES

Solution of posterior pituitary was introduced into obstetrics by Blair Bell and Hofbauer.<sup>42</sup> Its use is now largely restricted to the control of postpartum bleeding in the third stage of labor and to the prevention or control of hemorrhage in therapeutic abortions. In some clinics, both here and abroad, intranasal application or cautious use of small intramuscular doses following administration of castor oil and quinine is advocated for induction of labor. However, rupture of the uterus, fetal asphyxia or even death, laceration of the cervix with hemorrhage or infection, secondary atony of the uterus with thrombosis and embolism, and cardiac death from sudden overexertion have all occurred from the misuse of pituitary preparations during labor.<sup>43</sup> Its use during the second stage of labor, to hasten separation of the placenta and to decrease bleeding during the third stage, may lead to hourglass contraction of the uterus necessitating manual removal

41. Reynolds, S. R. M.: *Physiology of the Uterus*, New York, Paul B. Hoeber, Inc., 1939.

42. Bell, W. B.: *The Pituitary Body and the Therapeutic Value of the Infundibular Extract in Shock, Uterine Atony, and Intestinal Paresis*, Brit. M. J., 2: 1609, 1909. Hofbauer, J.: *Hypophysenextrakt als Wehenmittel*, Zentralbl. f. Gynäk., 25: 137, 1911.

43. Davis, M. E.: *The Use and Abuse of Ergot and Pituitary*, J. A. M. A., 109: 1631 (Nov. 13) 1937. Sharkey, J. A.: *Should Solution of Posterior Pituitary Be Used in the First and Second Stages of Labor?* *ibid.*, 115: 1315 (Oct. 19) 1940. Pendleton, G. F.: *Abuse of Solution of Posterior Pituitary During Early Labor*, *ibid.*, 115: 1318 (Oct. 19) 1940. DeLee, J. B.: *The Use of Solution of Posterior Pituitary in Modern Obstetrics*, *ibid.*, 115: 1320 (Oct. 19) 1940.

33. Heller, H.: *The Effect of the Hydrogen Ion Concentration on the Stability of the Anti-Diuretic and Vasopressor Activities of Posterior Pituitary Extracts*, J. Physiol., 96: 337 (Aug. 14) 1939.

34. Burgess, W. W.; Harvey, A. M., and Marshall, E. K., Jr.: *The Site of the Anti-Diuretic Action of Pituitary Extract*, J. Pharmacol. & Exper. Therap., 49: 237 (Oct.) 1933. Gershl, Isidore: *Reabsorption of Water During Pituitary Anti-Diuresis*, *ibid.*, 52: 231 (Oct.) 1934.

35. Stehle, R. L., and Bourne, W.: *The Effect of Pituitary Extract on the Secretion and Composition of the Urine*, J. Physiol., 60: 229 (July) 1925.

36. Molitor, H., and Pick, E. P.: *Ueber die Bedeutung des Gewehswassers für die Wirkung diuresisbeeinflussender Arzneimittel: I. Der Einfluss von Flüssigkeitsanreicherung auf die Stärke der Pituitrinwirkung*, Arch. internat. de pharmacodyn. et de therap., 35: 279, 1930.

37. Heller, H.: *The Action of the Anti-Diuretic Principle of Posterior Pituitary on the Urine Excretion of Anesthetized Animals*, J. Physiol., 98: 405 (Aug.) 1940.

38. Melville, K. I.: *Pressor and Oxytocic Fractions of Posterior Pituitary Extract; Comparative Effects on Blood Pressure and Intestinal Activity*, J. A. M. A., 106: 102 (Jan. 11) 1936.

39. Dodds, E. C.; Noble, R. L., and Smith, E. R.: *A Gastric Lesion Produced by an Extract of the Pituitary Gland*, Lancet 2: 918 (Oct. 27) 1934.

40. Knaus, Hermann: *Die periodische Fruchtbarkeit und Unfruchtbarkeit des Weibes*, Vienna, E. Maudrich, 1934. Robson, J. M.: *Recent Advances in Sex and Reproductive Physiology*, Philadelphia, P. Blakiston's Son & Co., 1934. Reynolds, S. R. M.: *The Effect of Certain Calcium Salts on the Rhythmically Contracting and Quiescent Uterine Fibers, with Observations on the Action of Posterior Pituitary Extracts*, Am. J. Physiol., 105: 358 (Aug.) 1933. Moir, Chas.: *Recording the Contraction of the Human Pregnant and Nonpregnant Uterus*, Tr. Edinburgh Obst. Soc., 1933-1934, p. 93, in Edinburgh M. J., August 1934. Adair, F. L., and Haugen, J. A.: *A Study of Suspended Uterine Muscle Strips *in Vitro**, Am. J. Obst. & Gynec., 37: 753 (May) 1939. McLellan, Archibald: *Response of Non-Gravid Human Uterus to Posterior Pituitary Extract*, Lancet 1: 919 (May 18) 1940.

and hence increasing the dangers of puerperal fever. The use of posterior pituitary extract during the puerperium to hasten involution is the practice of some obstetricians in the belief that poor involution increases the chances of pelvic infection. Others believe that it is bad practice to aggravate a uterus that tends to wall off infection by reduced activity.

In the normal parturient patient, posterior pituitary in therapeutic doses usually produces no effect on the blood pressure. In the patient with eclampsia or preeclampsia, however, there are marked rise in blood pressure and decrease in urine volume.<sup>44</sup> Dieckmann and Michel have suggested "the pituitrin cold pressor test" (repeated cautious injections of pitressin) as an aid in detecting potential toxemia and in differentiating preeclampsia from the other forms of toxemia.

Posterior pituitary or its pressor fraction is of greatest value in the treatment of diabetes insipidus. This condition is characterized by persistent polyuria, the urine being of low specific gravity, and polydipsia, which is secondary to the polyuria.<sup>45</sup> Both clinical and experimental studies support the view that diabetes insipidus is due to changes in the neurohypophysis resulting in loss of or diminution in the antidiuretic substance.<sup>46</sup> That the anterior lobe plays an important role in water metabolism is attested by the fact that complete hypophysectomy results in transient diabetes insipidus only. It has been suggested that the anterior lobe gives rise to a diuretic substance which normally antagonizes the antidiuretic action of the neurohypophysis. It is thought that this diuretic substance may act through the thyroid gland, probably through the intermediation of the thyrotropic principle of the anterior lobe.<sup>47</sup>

Other clinical uses for the pressor fraction are found in the treatment of paralytic ileus, in the allaying of postoperative distention<sup>48</sup> and in cholecystography, to reduce intestinal flatus.<sup>49</sup> The combination of pitressin with ephedrine has been advocated for the maintenance of blood pressure during spinal anesthesia.<sup>50</sup> The ephedrine, in addition to giving a transient rise in blood pressure, antagonizes the coronary constrictor action of the pitressin.<sup>50</sup> For the alleviation of the polyuria and polydipsia of diabetes insipidus, nasal insufflation of the dry powder has been used with success, while both clinical and experimental attempts have been made to prolong the action of subcutaneous or intramuscular injections by administering the pituitary preparation

with zinc salts or in oil.<sup>51</sup> Further work is required for a proper evaluation of these newer preparations.

#### DISEASES ASCRIBED TO HYPERSECRETION

In recent years, attempts have been made to associate preeclampsia and eclampsia with hypersecretion of the posterior lobe of the pituitary. However, attempts to demonstrate the presence of the active principles in the blood or urine of patients with these conditions have yielded variable results.<sup>52</sup> The possibility remains that the body becomes unusually sensitive to pituitary substances and support for this view comes from the work of Dieckmann and Michel, Lambillon and others.<sup>44</sup> Further study will be required to establish the role of the neurohypophysis in hypertension.<sup>53</sup>

#### HYPERSENSITIVITY TO POSTERIOR PITUITARY

Several cases of hypersensitivity to posterior pituitary have been reported.<sup>54</sup> The symptoms are those of shock: marked pallor, rapid pulse, fall in blood pressure, air hunger, sense of impending death and, in more severe cases, edema and semiconsciousness. These symptoms are alleviated by epinephrine.

#### CONCLUSION

While, perhaps, one still cannot assign with certainty any specific roles to the powerful principles of the posterior lobe, nevertheless, in recent years much evidence, both clinical and experimental, has accumulated which indicates that the pressor substance plays an important role in water metabolism.<sup>55</sup> In regard to the oxytocic fraction, opinion is still divided as to whether or not it is a factor in the initiation of uterine contractions during labor. Of interest in this respect is the report by Fisher and co-workers that in cats suffering from experimental diabetes insipidus there developed striking disturbances in the mechanism of parturition.<sup>56</sup> The wide use of solution of posterior pituitary and of preparations of various fractions from the posterior lobe in both surgery and obstetrics justifies the furtherance of experimental studies to establish the chemical composition of the active principles, to determine their mechanism of action and to discover their role in the normal economy of the body.

44. Dieckmann, W. J., and Michel, H. L.: Vascular Renal Effects of Posterior Pituitary Extracts in Pregnant Women, *Am. J. Obst. & Gynec.* **33**: 131 (Jan.) 1937. Lambillon, Joseph: Contribution expérimentale et clinique à l'étude de la physiologie posthypophysaire de la grossesse et de ses rapports avec la gestose éclamptogène, *Rev. belge sc. méd.* **10**: 1 (Jan.) 1938. de Valera, E., and Kellar, R. J.: On the Effects of Intravenous Vasopressin on the Toxemias of Pregnancy, *J. Obst. & Gynaec. Brit. Emp.* **45**: 815 (Oct.) 1938.

45. Richter, C. P.: The Primacy of Polyuria in Diabetes Insipidus, *Am. J. Physiol.* **112**: 481 (July) 1935.

46. (a) Fisher, Charles; Ingram, W. R., and Ranson, S. W.: Diabetes Insipidus and the Neurohumeral Control of Water Balance, *Ann Arbor, Mich., Edward Brothers, Inc.*, 1938. (b) Berlinger, W.: Diabetes insipidus bei entzündlich-fibrosen Atrophie der Neurohypophyse nach Unfall, *Endokrinologie* **20**: 305, 1938. (c) Baker, A. B., and Craft, C. B.: Bilateral Localized Lesions. The Hypothalamus with Complete Destruction of the Neurohypophysis in a Pituitary Dwarf with Severe Diabetes Insipidus, *Endocrinology* **26**: 801 (May) 1940. (d) Dandy, W. E.: Section of the Human Hypophyseal Stalk: Its Relation to Diabetes Insipidus and Hypophyseal Functions, *J. A. M. A.* **114**: 312 (Jan. 27) 1940.

47. Barnes, B. O.; Kegan, J. F., and Bueno, J. G.: Is There a Specific Diuretic Hormone in the Anterior Pituitary? *Am. J. Physiol.* **105**: 559 (Sept.) 1933. Keller, A. D.: Hypophyseal Thyrotropic Mechanism Essential for Occurrence of Diabetes Insipidus in Its Maximal Form, *Proc. Soc. Exper. Biol. & Med.* **26**: 787 (June) 1937.

48. Potter, P. C., and Mueller, R. S.: Value of Pitressin in Abdominal Surgery with Special Reference to Dosage and Technique, *Am. J. Surg.* **43**: 710 (March) 1939. Frazier, W. D.: Use of Pitressin for Control and Relief of Distention, *Am. J. Surg.* **36**: 672 (June) 1937.

49. Kirklin, B. R., and Sedorff, C. E.: Use of Pitressin in Cholecystography, *Proc. Staff Meet., Mayo Clin.* **14**: 502 (Aug. 9) 1939.

50. Chalkoff, J. S.: Efficacy of the Combination of Ephedrine and Pitressin as Preanesthetic Medication in the Control of Blood Pressure During Spinal Anesthesia, *Anesth. & Analg.* **19**: 121 (May-June) 1940.

51. Rutledge, D. I., and Rynearson, E. H.: Diabetes Insipidus: Treatment by Insufflation of Powdered Posterior Pituitary Substance, *Proc. Staff Meet., Mayo Clin.* **14**: 443 (July 12) 1939. Court, Donald, and Taylor, S. A.: Diabetes Insipidus Treated by Slowly Acting Pituitary Emulsion, *Proc. Roy. Soc. Med.* **32**: 1203 (Aug.) 1939. Greene, J. A., and January, L. E.: Diabetes Insipidus Treated by the Subcutaneous Administration of a Suspension of Pitressin Tannate in Oil, *J. A. M. A.* **115**: 1183 (Oct. 19) 1940. Stephens, D. J.: Zinc Salts and Oil in Prolongation of Therapeutic Effects of Pitressin in Experimental Diabetes Insipidus, *Proc. Soc. Exper. Biol. & Med.* **44**: 240 (May) 1940. Dolds, E. C.; Noble, R. L.; Rinderknecht, H., and Williams, P. C.: Prolongation of Action of the Pituitary Anti-Diuretic Substance and of Histamine, by Metallic Salts, *Lancet* **2**: 309 (Aug. 7) 1937.

52. Anselmino, K. J., and Hoffmann, F.: Ueber die pathologische-anatomischen Grundlagen einer gesteigerten f. Gynäk. **58**: 2363 (Oct. 6) 1934. Byrom, F. Alleged Pituitary Origin of the Eclamptic and Pre-Eclamptic "Toxemias" of Pregnancy, *Quart. J. Med.* **3**: 361 (July) 1934. Melville, K. I.: Anti-Diuretic Pituitary Substance in Blood, with Special Reference to the Toxemia of Pregnancy, *J. Exper. Med.* **65**: 415 (March) 1937. Teel, H. M., and Reid, D. E.: Occurrence of Anti-Diuretic Substance in Urine of Patients with Pre-Eclampsia and Eclampsia, *Endocrinology* **24**: 297 (March) 1939.

53. Liu, S. H.: Pathological States Produced by the Administration of Posterior Pituitary Pressor Principle, *Chinese M. J.* **55**: 448 (May) 1939.

54. McMann, Walter: Hypersensitivity to Solution of Posterior Pituitary, *J. A. M. A.* **115**: 1488 (Oct. 14) 1939. Pendleton, G. F.; Ball, W. G., and Rhode, William: Hypersensitivity to Pituitary Extract, *J. Missouri M. A.* **34**: 194 (June) 1937. Simon, F. A., and Ryder, C. F.: Hypersensitivity to Pituitary Extracts, *J. A. M. A.* **106**: 512 (Feb. 15) 1936.

55. Gersh, Isidore: Water Metabolism: Endocrine Factors, A Research and Nerv. & Ment. Dis., *Proc.* (1939) **20**: 436, 1940. Fisher, Ingram and Ranson.<sup>56</sup>

56. Fisher, Charles; Ranson, S. W., and Magoun, H. W.: Dystocia in Diabetes Insipidus, *Am. J. Obst. & Gynec.* **36**: 1 (July) 1938.



## The Chemical Laboratory

THE A. M. A. CHEMICAL LABORATORY HAS AUTHORIZED PUBLICATION  
OF THE FOLLOWING REPORT. PAUL NICHOLAS LEECH, Director.<sup>1</sup>

### CRYSTALLINE SULFATHIAZOLE

Chemical and pharmacologic data on the compound 2-(*p*-aminobenzenesulfonamido)-thiazole, for which the nonproprietary name sulfathiazole has been adopted by the Council on Pharmacy and Chemistry, were published by Fosbinder and Walter<sup>2</sup> in August 1939. Intense interest in sulfanilamide and its derivatives on the part of the medical profession prompted commercial production of sulfathiazole in quantities sufficient for thorough clinical evaluation. In June 1940, specimens of commercial sulfathiazole were presented to the A. M. A. Chemical Laboratory for examination at the request of the Council on Pharmacy and Chemistry. Preliminary investigation of the submitted brands of sulfathiazole by Dr. E. W. Schoeffel, a former member of the Laboratory staff, led to the discovery of a peculiarity in the melting characteristics of this compound. This information was transmitted to Dr. Theodore G. Klumpp, Chief, Drug Division, U. S. Food and Drug Administration, who instigated an investigation mentioned later. The melting points were determined by two methods: (a) the method given in the U. S. P. XI and (b) a method which involves observation of small quantities of material on an electrically heated stage under a microscope. Each method is susceptible of standardization against National Bureau of Standards calibrated thermometers.

The first of two specimens of sulfathiazole supplied by the Maltbie Chemical Company was found to melt at about 178 C.; the second was found to contain some crystals which melted at about 178 C., together with a bulk of material which melted at about 202 C. This information was in contrast to melting point data found for portions of specimens of sulfathiazole submitted by the Calco Chemical Division American Cyanamid Company,

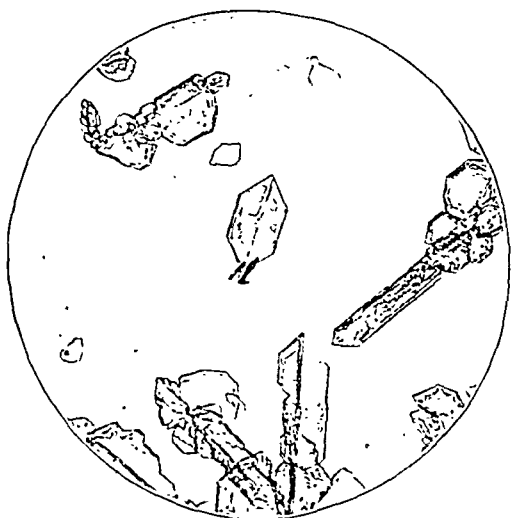


Fig. 1.—Sulfathiazole crystals with a melting point of about 175 C.

Merck & Co., Inc., and the Lederle Laboratories, Inc. It was found that each of these specimens melted at from 202 to 203 C., when heated according to the U. S. P. XI method. Close observation revealed a transient but characteristic phenomenon between 172 and 178 C. In each instance the column of solid within the heated capillary slumped very slightly and minute molten globules appeared; the latter seemed to wet the glass and resolidify almost immediately. Under the microscope, all these specimens were found to exhibit varying amounts of material

which melted at 172-178 C., some material which underwent a structural transformation in the solid state and finally melted at 200-203 C., and a preponderant amount of material which melted at 201-203 C.

Portions of each of the submitted specimens of sulfathiazole were recrystallized from boiling 95 per cent ethyl alcohol. Long, acicular crystals and massive, hexagonal, platelike crystals were obtained. The two crystalline forms were dried and examined under the microscope on the electrically heated stage. The needle-like crystals were found to melt at 202-203 C. The

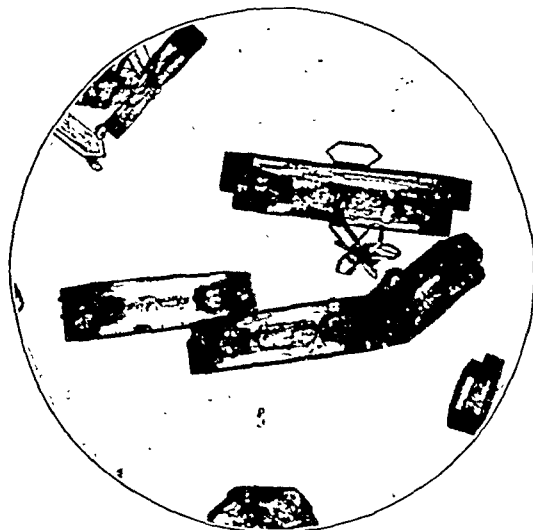


Fig. 2.—Sulfathiazole crystals (pseudomorphic habit) with a melting point of about 202 C.

platelike crystals were found to behave variously as follows: (1) Some of the crystals melted at 172-175 C. and remained molten; (2) some of the crystals melted at 172-175 C., followed by resolidification of the molten mass, which finally remelted at 200-203 C.; (3) some of the crystals exhibited a structural transformation in the solid state at 172-175 C. and finally melted at 201-203 C. From the latter observation it was apparent that an alteration in the structure of the crystals, induced by heat, resulted in a higher melting point. Accordingly, the original specimen of sulfathiazole which had been found to melt completely at about 175-178 C. was placed in an oven at 105 C. for five hours. The melting point of the specimen was then found to be from 202 to 203 C., with only a few crystals which showed transition in the solid state at 172-178 C.

The foregoing data on sulfathiazole indicated that this compound exhibits dimorphism, or the ability to exist in the solid state in two crystalline configurations. The observations have been confirmed by Grove and Keenan<sup>3</sup> in the chemical laboratories of the U. S. Food and Drug Administration, who have reported additional chemical data and optical properties of the two crystalline forms.

Since sulfathiazole is soluble in both acids and bases, it was decided to examine crystals of sulfathiazole precipitated from acid solution by the addition of sufficient base and crystals of sulfathiazole precipitated from basic solution by the addition of sufficient acid. It was thought that two crystalline modifications might be obtained. It was found, however, that the crystalline habit of sulfathiazole in the form which melts at 172-175 C. varies with the method of precipitation. Crystals of sulfathiazole obtained by neutralization of a clear hydrochloric acid solution of sulfathiazole appear as thin hexagonal plates (fig. 1). These crystals melt unchanged at 172-175 C. and apparently resist transformation in the solid state on prolonged heating at 100-105 C. Crystals of sulfathiazole obtained by neutralization of a clear sodium hydroxide solution of sulfathiazole appear in the form of thick, elongated hexagonal plates (fig. 2). When heated rapidly, these crystals melt at 172-175 C. However, they readily undergo a transition in the solid state at this temperature, and

1. This was the last report prepared under Dr. Leech's direction before his death suddenly on January 14.

2. Fosbinder, R. J., and Walter, L. A.: Sulfanilamide Derivatives of Heterocyclic Amines, *J. Am. Chem. Soc.* 61: 2032 (Aug.) 1939.

3. Grove, D. C., and Keenan, G. L.: The Dimorphism of Sulfathiazole, *J. Am. Chem. Soc.*, to be published.

the resulting pseudomorphic habit melts at 201-203 C. This same transformation may be produced by prolonged heating of the thick, elongated plates at a temperature of 100-105 C. without change in the gross appearance of the crystal form.

The method used in the preparation of the two differently melting types of sulfathiazole is as follows:

(a) Place 25 Gm. of sulfathiazole and 250 cc. of distilled water in a 500 cc. beaker. Stir the mixture mechanically, and slowly add 20 cc. of concentrated hydrochloric acid. Continue to stir the mixture for several minutes and filter the resulting solution. Slowly neutralize the constantly stirred filtrate with 2 normal sodium hydroxide. Collect the glistening white precipitate on a Buchner funnel and wash the crystals with distilled water until chlorides are absent from the washings. Spread the thoroughly drained product on a large watch glass and dry it in an oven maintained at 100-105 C. for from two to three hours. The melting point of the product is from 172 to 175 C.

(b) Place 25 Gm. of sulfathiazole and 250 cc. of distilled water in a 500 cc. beaker, stir mechanically, and slowly add 4 Gm. of sodium hydroxide dissolved in 25 cc. of water. Filter the resulting solution and neutralize the filtrate with normal hydrochloric acid. Collect, wash and dry the heavy precipitate as described but continue to heat for twelve hours at 100-105 C. The melting point of the product is from 201 to 203 C.

That a difference in pharmacologic activity exists between the two crystalline modifications as striking as the melting point difference is questionable. Accordingly, the toxicity of quantities of each of the two differently melting types of sulfathiazole, prepared as described, is being investigated by Dr. Raymond N. Bieter of the Department of Pharmacology of the University of Minnesota Medical School, who will report his results in a separate publication.

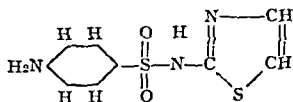
## Council on Pharmacy and Chemistry

### NEW AND NONOFFICIAL REMEDIES

THE FOLLOWING ADDITIONAL ARTICLES HAVE BEEN ACCEPTED AS CONFORMING TO THE RULES OF THE COUNCIL ON PHARMACY AND CHEMISTRY OF THE AMERICAN MEDICAL ASSOCIATION FOR ADMISSION TO NEW AND NONOFFICIAL REMEDIES. A COPY OF THE RULES ON WHICH THE COUNCIL BASES ITS ACTION WILL BE SENT ON APPLICATION.

PAUL NICHOLAS LEECH, Secretary.

**SULFATHIAZOLE.**—2-sulfanilamidothiazole. —2-sulfanilylaminothiazole. —2-(*p*-aminobenzenesulfonamido) thiazole. —4-aminobenzenesulfonyl-2-aminothiazole. — $C_8H_8O_2N_4S_2$ . —Sulfathiazole has the following structural formula:



[It may be prepared by the condensation of *p*-acetylaminobenzene-sulfonylchloride with 2-aminothiazole in pyridine. The compound 2-(*p*-acetyl-amino-benzenesulfonamido) thiazole separates on dilution of the reaction mixture with water and is subsequently hydrolyzed with hydrochloric acid. Sulfathiazole is then isolated by neutralization of the acid solution to congo red and purified by recrystallization from alcohol.

**Actions and Uses.**—Sulfathiazole has been reported to show definite chemotherapeutic effects in experimental infections in mice produced by the inoculation of pneumococci, meningococci, beta hemolytic streptococci, staphylococci, *Escherichia coli* or the virus of lymphogranuloma venereum. Comparative tests have shown that sulfathiazole is equal to sulfapyridine in its chemotherapeutic effects in experimental pneumococcal infections in mice and that it is somewhat superior to sulfanilamide or sulfapyridine in the control of experimental infections in mice produced by *Staphylococcus aureus* or *E. coli*.

Its mode of action is probably similar to that of sulfanilamide, namely to render the blood, spinal fluid, urine and other tissue fluids unfavorable as a medium for supporting the active multiplication of susceptible bacteria. In consequence, tissue invasion by these organisms may be prevented, the production of toxic substances reduced and the antibacterial immune mechanisms of the host permitted to complete the recovery from infection.

Sulfathiazole has been used primarily in the treatment of infections due to the pneumococcus, i. e. pneumococcal pneumonia, and of severe infections due to *Staphylococcus aureus*. There is evidence to show that the drug is chemotherapeutically effective in the control of tissue infections produced by *E. coli*; and it is known on the basis of clinical tests that the drug is an effective chemotherapeutic agent in the treatment of gonorrhea in the male. Its use in urinary tract infections produced by *E. coli*, *Streptococcus faecalis*, *Staphylococcus aureus* or *Bacillus pyocyaneus* is still in the experimental stage.

Sulfathiazole resembles sulfanilamide in certain of its pharmacologic effects. In most patients it is rapidly absorbed when administered by mouth, maximum concentrations of the drug in the blood being obtained in three to six hours after the administration of a single dose. It is fairly evenly distributed throughout most of the body tissues with the exception that it does not pass readily into the spinal fluid. In the tissues a certain proportion of the drug is conjugated to the therapeutically inactive acetyl derivative. The degree of conjugation is, as a rule, slightly greater than that noted for sulfanilamide, but generally less than that for sulfapyridine. It is excreted rapidly by the kidneys and because of this it is sometimes difficult to maintain adequate concentration of the drug in the blood and tissues. If kidney function is impaired the excretion of sulfathiazole will be reduced and the drug will accumulate in the blood and tissues.

In the urine considerably less sulfathiazole is found in the conjugated form than has been generally noted for either sulfanilamide or sulfapyridine. The excretion of the drug is generally almost complete within twenty-four hours after the administration of a single dose of the compound.

**Toxicity.**—The toxic manifestations noted in the course of sulfathiazole therapy are similar to those previously noted in the course of therapy with sulfanilamide or sulfapyridine. These untoward effects are unpredictable in their occurrence and are considered to be the result of an idiosyncrasy to the drug.

Patients who are receiving this drug should be seen daily by their physician in order that any possible toxic effects arising in the course of the administration of sulfathiazole may be noted and appropriate steps taken to eliminate the drug.

Sulfathiazole causes less nausea, vomiting and dizziness than does sulfapyridine; mental disturbances or psychoses are uncommon. Questionable so-called peripheral neuritis has been reported. Cyanosis is generally mild if present, and acidosis has not been noted. Drug fever is very common in the course of treatment with sulfathiazole, having been observed in about 10 per cent of the patients who are receiving this drug. It generally occurs between the fifth and ninth days of treatment but may occur at any period. Drug rashes with or without fever are more frequent in the course of sulfathiazole therapy than when sulfapyridine is being prescribed. The drug may produce all types of rashes. Urticarial or nodular rashes resembling erythema nodosum are often seen.

Hepatitis is rare. Leukopenia with granulocytopenia has been noted either early or late in the course of therapy. Acute agranulocytosis has not as yet been reported as occurring in the course of therapy with this drug but undoubtedly will occur. Mild or severe acute hemolytic anemias are uncommonly seen. Microscopic or gross hematuria has occurred in about 2.5 per cent of the patients who have received this drug, and anuria with azotemia has been observed. The hematuria and more severe evidence of kidney damage may be due in certain instances to the formation of acetylsulfathiazole crystals and renal calculi which block the renal tubules or even the renal pelvis and ureters, but in other patients these toxic manifestations seem to result from a direct toxic reaction of the drug on the renal epithelium. Because of these renal toxic reactions it is important to keep the urinary output above 1,000 cc. in the course of therapy with sulfathiazole.

A curious toxic manifestation which has hitherto been unreported in the course of therapy with sulfanilamide or sulfapyridine, and which has been noted frequently in the course of sulfathiazole therapy, is the injection of the scleras and conjunctivas, which when severe may give the appearance of the disease "pink eye." Mild to severe arthralgia may accompany the fever and rashes which are produced by sulfathiazole.

When fever, rash, hepatitis, granulocytopenia, acute hemolytic anemia, hematuria with oliguria, injection of the scleras and conjunctivas or other serious toxic manifestations occur the drug should be stopped and fluids forced in order that sulfathiazole may be eliminated from the body as rapidly as possible.

As far as is known at the present time, sulfathiazole can be used concurrently with any other drugs, with the possible exception of magnesium sulfate or other saline laxatives. It is not

necessary to try to eliminate sulfur-containing foods from the diets of patients who are receiving sulfanilamide, sulfapyridine or sulfathiazole.

**Dosage.**—Sulfathiazole is poorly soluble and hence must be administered by the oral route. Sulfathiazole should not be used in the therapy of any type of meningitis, because the drug does not pass over readily into the spinal fluid.

In the treatment of pneumococcal pneumonia in adults (patients over 14 years of age) the initial dose of sulfathiazole should be 4 Gm., to be followed by 1 Gm. every four hours day and night until the patient's temperature has been normal for seventy-two hours. The drug should then be discontinued. In children ill with pneumococcal pneumonia the initial dose should be based on 0.15 Gm. per kilogram (up to 25 Kg. body weight) and the total daily dose is calculated on the same basis. The total daily dose should be divided into four equal parts and administered at six hour intervals until the temperature has been normal for thirty-six hours. The drug should then be stopped.

It is to be remembered that surgical measures, both supportive and operative, must be used in the treatment of staphylococcal infections in conjunction with sulfathiazole whenever indicated. Surgical drainage of purulent foci must be effected, because while the drug may halt the invasive manifestations of staphylococcal infection it will not by itself cure areas of localized infections, and a flare-up of the infection from such areas is likely to occur if they are not properly drained.

The drug should not be used in the treatment of minor staphylococcal infections such as localized boils and small carbuncles or in mild furunculosis. In large boils or carbuncles, the initial dose for adults should be 4 Gm., followed by 1 Gm. every four hours day and night for from five to seven days. In diffuse staphylococcal cellulitis, lymphangitis or acute osteomyelitis, in adults 4 Gm. should be given as an initial dose, to be followed by doses of 1.5 Gm. every four hours day and night as long as evidence of a spreading infection continues. The dose should then be reduced to 1 Gm. every four hours day and night and continued as indicated. In staphylococcal bacteremia the initial dose for adults should be 4 Gm. followed by 1.5 Gm. every four hours day and night until the temperature has been normal for forty-eight hours. The dose may then be reduced to 1 Gm. to be given every four hours day and night for fourteen days, at which time the dose may be reduced to 0.5 Gm. every four hours day and night to be continued for a minimum of fourteen days. In severe staphylococcal infections in children, the initial dose should be calculated on the basis of 0.2 Gm. per kilogram of body weight (up to 20 Kg. of weight). The total daily dose is calculated on the same basis and should be divided into the six parts, given at four hour intervals day and night until the temperature has been normal for forty-eight hours. Then the dose may be cut by one third and treatment should be continued at this level of dosage for fourteen days, at which time the current dose may be reduced by one half. In staphylococcal bacteremia there is a great possibility that a relapse will occur unless prolonged treatment with the drug is employed. In chronic staphylococcal infections, such as osteomyelitis, not enough information is available to warrant definite instructions as to the use of the drug.

It is very important to control the administration of sulfathiazole by determining its concentration in the blood of patients who are receiving it. In pneumonia, concentrations of from 4 to 6 mg. per hundred cubic centimeters are desirable. In severe or bacteremic staphylococcal infections, concentrations of 7 to 10 mg. per hundred cubic centimeters of the drug in the blood should be sought. These may both be determined by employing Marshall's method (*J. Biol. Chem.* 128:537 [May] 1939). The recovery of sulfathiazole from the blood is practically quantitative when a 1 to 50 dilution of the blood is used and the determination read in a photoelectric colorimeter. With an ordinary colorimeter and using a 1 to 20 dilution of the blood, the recovery of sulfathiazole is not quantitative and a factor of 15 per cent should be added to the reading obtained. This factor holds for concentrations of from 1 to 10 mg. per hundred cubic centimeters of the drug in the blood.

Sulfathiazole occurs as a white, practically odorless and tasteless crystalline powder. It is soluble in glacial acetic acid and in pyridine, slightly soluble in ethyl, methyl and isopropyl alcohols, very slightly soluble in water, and insoluble in benzene, chloroform, ether, ethyl acetate and ethylene dichloride. It is soluble in dilute mineral acid solutions and alkali metal hydroxide and carbonate solutions; slightly soluble in alkali metal bicarbonate solutions. It is soluble in hot water and in hot ethyl, methyl and isopropyl alcohols; moderately soluble in hot acetone. When sulfathiazole is heated in a capillary tube, slight sintering occurs at from 168 to 175 C., and the substance melts at from 200 to 203.5 C., with slight decomposition. [When the melting point is determined using a micromelting point stage, there may be indicated the presence of two crystalline forms having separate melting points. Crystals melting about 172-173 C. may be observed to undergo a transition in the solid state at this temperature and, if

melted, may recrystallize (on scratching or seeding with a crystal having a melting point of 200-203.5 C.) in a form having a melting point of 200-203.5 C.]

Place approximately 0.1 Gm. of sulfathiazole in a small test tube containing a thermometer. Heat the tube cautiously on a sand bath: the material melts, a brown color develops, the product decomposes rapidly at about 230 C. (distinction from sulfanilamide and sulfapyridine), the odor of hydrogen sulfide is evolved, and a stain is produced on a strip of moist lead acetate paper held at the mouth of the tube. Dissolve about 20 mg. of sulfathiazole in 0.25 cc. sodium hydroxide solution and 5 cc. of water; add copper sulfate solution dropwise; with shaking a grayish purple precipitate forms (distinction from sulfapyridine, which yields a green precipitate, and sulfanilamide, which yields a blue solution or precipitate). Boil 0.3 Gm. of sulfathiazole with 3 cc. of glacial acetic acid, cool, add 0.2 cc. of acetic acid anhydride and boil for three minutes. Cool the solution, add 3 cc. of water, mix and allow to stand for ten minutes; filter, wash the precipitate with water and dry at 100 C.; the melting point of the acetyl sulfathiazole obtained is from 265 to 269 C.

Dissolve 0.5 Gm. of sulfathiazole in 25 cc. of hot alcohol: the solution is clear and colorless. Dissolve 1 Gm. of sulfathiazole in 20 cc. of water containing 0.25 Gm. of sodium hydroxide: the solution is clear and colorless. Dissolve 0.5 Gm. of sulfathiazole in 5 cc. of hot dilute hydrochloric acid: the solution is clear and colorless. Cool the acid solution, add 5 cc. of concentrated hydrochloric acid and allow to stand: a feathery white precipitate forms.

Digest 1.5 Gm. of sulfathiazole, accurately weighed, with 75 cc. of water at 70 C. for ten minutes; cool and filter: the saturated aqueous solution of sulfathiazole is neutral or slightly acid ( $pH = 5.6$  to  $6.3$ ) to litmus. To 25 cc. of the filtrate add 5 drops of nitric acid and 1 cc. of silver nitrate solution: the turbidity produced does not exceed that produced in a control test by 0.25 cc. of fiftieth-normal hydrochloric acid. Evaporate another 25 cc. portion of the filtrate to 10 cc., cool, filter, if necessary, and add 0.5 cc. of normal hydrochloric acid and 1 cc. of barium chloride solution: the turbidity produced does not exceed that produced in a control test by 0.1 cc. of one-hundredth normal sulfuric acid.

Incinerate 1 Gm. of sulfathiazole, accurately weighed, in a porcelain vessel: the residue amounts to not more than 0.05 per cent. Add to the residue on incineration 1 cc. of hydrochloric acid and 5 drops of nitric acid; evaporate to dryness on the steam bath; warm the residue with 1 cc. of normal hydrochloric acid, add 40 cc. of distilled water, filter and add 10 cc. of freshly prepared hydrogen sulfide solution: the darkening produced is not greater than that produced in a control test made with 0.02 mg. of lead.

A 0.1 Gm. portion of sulfathiazole will pass the test for arsenic given in the U. S. P. XI, page 436.

Dry about 1 Gm. of sulfathiazole, accurately weighed, at 100 C. for five hours: the loss does not exceed 0.5 per cent.

The sulfur content of dried sulfathiazole is not less than 24.7 per cent nor more than 25.3 per cent. The nitrogen content of dried sulfathiazole is not less than 16.2 per cent nor more than 16.6 per cent.

Dissolve about 0.5 Gm. of sulfathiazole, accurately weighed, in 50 cc. of water and 5 cc. concentrated hydrochloric acid; cool to 15 C., and titrate with tenth-molar sodium nitrite solution. The endpoint is the first immediate blue streak obtained when a glass rod dipped into the solution is drawn across a smear of starch-iodide paste on white filter paper. The solution should retain this endpoint for thirty seconds. The use of starch-iodide paste rather than starch-iodide paper is necessary for accurate results. Each cubic centimeter of tenth-molar sodium nitrite corresponds to 0.02553 Gm. of sulfathiazole: the amount of sulfathiazole found corresponds to not less than 99.5 nor more than 101.0 per cent, calculated on the dried basis.

**NOTE.**—The starch-iodide paste is prepared as follows: Boil 430 cc. of water in a beaker set in an oil bath; add 3 Gm. of potassium iodide dissolved in 15 cc. of water, followed by 7.5 Gm. of zinc chloride dissolved in 30 cc. of water. While the solution is boiling, add, with stirring, a slurry of 20 Gm. of potato starch in 100 cc. of cold water. Continue to boil for two minutes, then cool and store the paste in tightly stoppered bottles. The starch-iodide paste must show a definite blue streak when a glass rod dipped in a solution of 1 cc. of tenth-normal sodium nitrite and 10 cc. hydrochloric acid dissolved in 1 liter of water is drawn across a smear of the paste; otherwise, fresh paste must be prepared.

The tenth-normal sodium nitrite solution must be standardized against pure sulfanilic acid by a similar procedure.

A fact which explains slightly high results is that the endpoint is not as satisfactory when assaying sulfathiazole by the nitrite method as that obtained in the assay of sulfanilamide or sulfapyridine.

**Sulfathiazole-Lederle.**—A brand of sulfathiazole-N. N. R. Manufactured by the Lederle Laboratories, Pearl River, N. Y. Patents pending. No U. S. trademark.

*Tablets Sulfathiazole-Lederle, 0.5 Gm. (7.7 grains).*

**Sulfathiazole-Maltbie.**—A brand of sulfathiazole-N. N. R. Manufactured by the Maltbie Chemical Company, Newark, N. J. U. S. patent applied for. No U. S. trademark.

*Tablets Sulfathiazole-Maltbie, 0.5 Gm. (7.7 grains).*

**Sulfathiazole-Merck.**—A brand of sulfathiazole-N. N. R. Manufactured by Merck & Co., Inc., Rahway, N. J. U. S. patent applied for. No U. S. trademark.

*Tablets Sulfathiazole-Merck, 0.5 Gm. (7.7 grains).*

**Sulfathiazole-Squibb.**—A brand of sulfathiazole-N. N. R. Manufactured by E. R. Squibb & Sons, New Brunswick, N. J. Patent application pending.

*Tablets Sulfathiazole-Squibb, 0.5 Gm. (7.7 grains).*

**Sulfathiazole-Winthrop.**—A brand of sulfathiazole-N. N. R. Manufactured by the Winthrop Chemical Co., Inc., New York. U. S. patent applied for. No U. S. trademark.

*Tablets Sulfathiazole-Winthrop, 0.5 Gm. (7.7 grains)  
Tablets Sulfathiazole-Winthrop, 0.25 Gm. (3.86 grains).*

# THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

535 NORTH DEARBORN STREET - - - CHICAGO, ILL.

Cable Address - - - - "Medic, Chicago"

Subscription price - - - - Eight dollars per annum in advance

*Please send in promptly notice of change of address, giving both old and new; always state whether the change is temporary or permanent. Such notice should mention all journals received from this office. Important information regarding contributions will be found on second advertising page following reading matter.*

SATURDAY, JANUARY 25, 1941

## THE NATIONAL EMERGENCY AS A PRETEXT FOR COMPULSORY HEALTH INSURANCE

Last week THE JOURNAL commented editorially on a recommendation made by Governor Olson of California to the California legislature that California adopt a system of universal compulsory health insurance. That recommendation was apparently based on inadequate study and revealed a failure to appreciate many factors intimately involved in the recommended scheme for medical care. Now comes a recommendation by Governor Lehman of New York in a special message to the New York legislature on January 14, in part as follows:

Your legislative commission on medical care and health insurance will report to you at this session. I repeat again that I am very much in sympathy with the principle of health insurance to take care of the medical and hospital needs of those with subnormal incomes. I hope that in the near future such individuals in our state and throughout the nation will be protected against the hazards of illness by a federal insurance system integrated with the federal social security program. I recommend that the report of your committee be given careful consideration.

Governor Lehman's recommendation forecasts a report which is to emanate shortly from the legislative commission on medical care and health insurance. The governor himself, however, notwithstanding some statements in the past, seems to favor compulsory federal sickness insurance.

Significant of the legislative thinking in New York, reflecting as it undoubtedly does the pressures of the health insurance groups, is a statement released January 7 by Justice R. Foster Piper of Erie County, retiring chairman of the special joint legislative committee for revision of the insurance law, of which he has been chairman since its creation in 1937. Justice Foster stated in part:

In my opinion, if the medical expense indemnity corporations do not fill this need (care of the public's medical service wants) eventually the state of New York must go all the way and provide for health insurance.

If, after a few years, it is found these corporations are not set up and functioning effectively, there appears to be nothing left to do except to establish state health insurance.

This year advocates of measures for health insurance are using the military emergency as added pressure. All sorts of extraneous matters are being plausibly advanced as supplementary to preparedness. There is a drive toward hasty enactment of new proposals into law, without giving them the acid test of argument and evaluation that could reasonably be anticipated in more normal times. Moreover, many agencies that ordinarily could be expected to be vigilant in opposing ill considered legislative proposals will be so engrossed in making workable features of the national defense within their particular domains that they will have neither the time nor the facilities for added attention to medical matters. The psychology engendered by war is already being used to stigmatize unfavorably efforts in opposition to certain proposals that in other, more thoughtful, times would be deemed praiseworthy and in the public interest.

Health insurance proponents begin their arguments with the statement that national defense cannot and will not reach its peak until measures are advanced that will enable the attainment of the optimum in the health of those who will eventually comprise the armed forces. Then they make the same statement for the population in general. The desirability of good health for all cannot be disputed. With careless disregard of minor premises and conclusions the argument continues to the general effect that our present system of medical care is inadequate and cannot produce the optimum in health conditions called for by the emergency. Resort must therefore be had, they insist, to a system of health insurance.

The future will tell how effective such argument will be with the legislatures and with the people. The signs are ominous for the continuation of a high quality of medical care and for respect of the rights of the people in relation to their health. A determined drive is on by health insurance fanatics to capitalize on the opportunity now presented by the emergency. Opposed to them are the forces of scientific professional medicine. Opposed also is the vastness of the funds they seek and the greater need for funds of the military and naval agencies needed in emergency.

But these advocates of health insurance go to extraordinary lengths to attain their ends. Some do not hesitate to place the achievement of their social objectives above the defense needs of the nation.

In Washington State in the last general election in November were a hundred or more initiative proposals which the electorate were called on to pass. One was a so-called "Senior Citizens Grants Act." As far as the ballot title was concerned, the sole basis of the individual voter's information as to what he was passing

on, this measure purported only to grant a monthly income of \$40 to persons 65 or over and to provide burial expenses. The measure was adopted by the voters. Hidden away in the measure was section 15, which read:

In addition to Senior Citizen Grants, the Department shall provide for those eligible medical, dental, surgical, optical, hospital and nursing care by a doctor of recipient's own choosing. . . .

So now in the state of Washington for one part of the population there is state medicine—after a fashion. This measure covers those over 65 years of age. Next will come efforts to reduce the age limit and to include more and more of the population.

### PERIPHERAL NEURITIS DUE TO SULFONAMIDE COMPOUNDS

The pharmacologic literature on various chronic toxic reactions with sulfonamide derivatives in the experimental animal has been scarce and unsatisfactory; indeed, many physicians believe that at least some of these phenomena cannot be produced experimentally. Thus there has occurred a tendency to try new derivatives clinically before satisfactory pharmacologic evidence has accumulated.

Among the reasons for this attitude is the fact that experiments on the acute toxicity of these drugs have been taken as a standard far too rigidly for the repeated administration of the drugs to man. The toxicity of single doses is not evidence of chronic toxicity. Pharmacologists have seldom given sufficient consideration to experiments involving long-continued administration of remedies. Gradually, however, this dearth of experiments is being rectified.

As most of the experimental work involving the therapeutic action of these drugs has been conducted on mice, rats and rabbits, it is not surprising that these species were the first to be used in "chronic" toxicity experiments. However, the failure of any particular toxic manifestation to appear after long use does not mean that it cannot be produced by experimental methods. It is more apt to mean that it should be looked for in some other species of animal. Until all available species of animals have been studied, one cannot say that any particular symptom of chronic toxicity cannot be produced experimentally.

In the experiments of Bieter, Baker, Beaton, Shaffer and Seery<sup>1</sup> a significant approach has been made on the question of experimental peripheral neuritis. Their confirmation of the pathologic studies of Nelson<sup>2</sup> on sulfanilamide strengthens the claim that the chicken is

a good test animal for peripheral neuritis with the sulfonamide group of drugs. Even if the chicken should be shown to be one hundred times more sensitive to this pathologic reaction than man—and as a guess this figure does not seem to be out of proportion at present—this species may serve a useful purpose in helping to determine the comparative safety of a given drug in the series. Up to the present time this has been impossible.

Turning now to the drugs that have been studied by the Minnesota investigators, one can say that the clinical evidence concerning peripheral neuritis following the administration of sulfanilamide and sulfapyridine—the two least harmful of the drugs in their series—is certainly not extensive. Uliron and sulfamethylthiazole appear at present to be capable of producing this injury in man too frequently to warrant their routine clinical use.

The most important question raised by their work concerns sulfathiazole. Their experiments indicate that this drug can produce more injury than either sulfanilamide or sulfapyridine. What does this mean in terms of clinical medicine? Bieter, Baker and their collaborators support their belief that this drug may produce symptoms of injury by reporting what appears to be quite likely a case of peripheral neuritis in man after administration of this drug. True an extremely long period of administration of the drug was used in this case. With certain persons, however, this is not necessarily a procedure to be condemned. In these instances it may be the lesser risk for the patient.

One other point comes to mind in connection with clinical peripheral neuritis: Cottrell<sup>3</sup> has recently shown that apparently normal peripheral nerve trunks in man show definite changes of a degenerative nature which occur with age. In the group of nerves she has studied, namely the median, femoral, sciatic and common peroneal, these changes occur first in the sciatic. Possibly changes of this nature may make a nerve more susceptible to the toxic neurotropic action of these drugs.

The ultimate answer to the various questions concerning peripheral neuritis with the sulfonamide group of drugs requires much more experimental and clinical study. This experimental approach should be continued and extended. Perhaps even more desirably, physicians should watch for this toxic manifestation as well as for all others to be observed with this form of therapy. When all the untoward reactions have been studied thoroughly and reported, the information will be valuable in the chemical approach toward new compounds that possess a minimum of this and other toxic manifestations.

1. Bieter, R. N.; Baker, A. B.; Beaton, J. G.; Shaffer, J. M., and Seery, T. M.: A Preliminary Report on the Nervous Injury Produced by Sulfanilamide and Its Derivatives in the Chicken, in press.

2. Nelson, A. A.: Histopathological Changes in Hens and Rabbits Following Administration of Sulfanilamide and Sulfanilyl Sulfanilamide (Di-Sulfanilamide), Pub. Health Rep. 54:106 (Jan. 27) 1939.

3. Cottrell, Lillian: Histologic Variations with Age in Apparently Normal Peripheral Nerve Trunks, Arch. Neurol. & Psychiat. 43:1138 (June) 1940.

## Current Comment

### HEALTH ACHIEVEMENTS IN WISCONSIN

The State Medical Society of Wisconsin has published a graphic pamphlet entitled "Health Achievements in Wisconsin." The typography and numerous illustrations make the statement especially attractive. The first picture is a map of the United States in which North Dakota, South Dakota and Wisconsin are numbered 1, 2 and 3 in solid black against a white background. Wisconsin was rated by the National Resources Board as the third healthiest state in the United States. The picture of a girl reading comfortably in a hospital bed calls attention to the fact that hospitals are as available in Wisconsin as they are in the state of New York. Pictures of water works, private wells, tourists' cabins, summer resorts, rivers, lakes and packing plants emphasize that Wisconsin protects the public health through the sanitary regulation of hotels, restaurants and barber shops and makes vacationing safe. There are fewer typhoid deaths in Wisconsin than in any other state in the United States. The second section of the pamphlet depicts "Medical Education and Training." Various phases in the life of a medical student are shown in a series of pictures. The third section points out the "Problems on Which Medicine Is Now Working." The state medical society, the state board of health and the industrial commission have done well in bringing so vividly to the front the health achievements in Wisconsin. A brochure of this type will no doubt indicate to the legislators of the state that conditions of health and medical care in Wisconsin are not so abysmally deficient as some proponents of a new order have depicted them.

### MEDICAL CARE FOR INDIGENT IN PENNSYLVANIA

The Medical Society of the State of Pennsylvania has for several years conducted, in cooperation with relief authorities, an extensive system of providing medical care to recipients of varying forms of state public assistance. This plan provides for "free choice, personal relationships, professional management, and fee basis for payment." The demand for professional service has greatly increased since Sept. 15, 1938, but no proportionate increase in the state funds has been made in the meantime. There are more than four thousand Pennsylvania physicians who have entered into an agreement to provide service through this plan. A recent report by Walter F. Donaldson,<sup>1</sup> secretary of the Medical Society of the State of Pennsylvania, says:

It was commonly claimed that while the total number of persons on direct relief due to unemployment has been materially reduced in Pennsylvania during recent months because of national defense and other sources of increasing employment, the fact remains that the physically handicapped, chronically ill, and persons of low resistance not desirable for reemployment continue their requests for medical service on an increasing scale as the knowledge of the existence of the service and expressions of satisfaction with it continue to spread.

<sup>1</sup> Donaldson, W. F.: Officers' Department, Pennsylvania M. J. 44: 495 (Jan.) 1941.

The funds available in the city of Philadelphia, which in 1938 were sufficient to pay a reduced fee schedule in full, by June 1940 met only 31 per cent of the fees.

### CONGRESS ON MEDICAL EDUCATION AND LICENSURE

Elsewhere in THE JOURNAL<sup>1</sup> appears the program of the Congress on Medical Education and Licensure sponsored, since 1905, by the Council on Medical Education and Hospitals of the American Medical Association. In these conferences the Federation of State Medical Boards actively participates. This year special emphasis is placed on medical preparedness as it affects the training of physicians. Other topics to be presented are the adjustment of medical education to social demand, the contribution of liberal education to professional training, the educational purpose of the standard nomenclature of disease, and the education of the Negro physician. Of particular interest to members of licensing boards will be papers dealing with the legal status of physicians and the enforcement of medical practice laws. All who may be interested are invited to attend.

### RADIO INTERFERENCE CAUSED BY DIATHERMY

Standards for reducing interference with radio communications resulting from the use of diathermy apparatus are sorely needed. The Federal Communications Commission recently held an informal engineering conference in Washington with representatives of the medical profession and of the manufacturers of electro-medical equipment to consider this subject. The medical profession was officially represented by members of the Council on Physical Therapy of the American Medical Association. In this conference the spokesman for the commission said that the commission recognized the importance of diathermy for the treatment of human ills and reiterated the desire of the commission to cooperate with the medical profession and with the manufacturers. At the Inter-American Radio Communication Conference, Santiago, Chile, in 1940 it was decided that countries in the Western Hemisphere "shall adopt measures to suppress or alleviate as much as possible interference caused by apparatus or equipment which may generate or radiate radiofrequency currents capable of interfering with or adversely affecting the reception of radio transmissions." One method to eliminate interference is to design diathermy apparatus to operate on definite frequencies and allocate these channels for this purpose only. The spokesman for the manufacturers asked for the allocation of three bands corresponding approximately to 23, 11.5 and 7.67 meters, the width of the bands to be comparable to ten broadcast channels at 23 and 7.6 meters and forty channels at 11.5 meters or sixty broadcast channels in all. Representatives of the commission felt that this request would not be granted because it required the setting aside of too many valuable channels of communication. The commission urged rather that apparatus be manufactured which would operate on one channel of communication without exten-

<sup>1</sup> Organization Section, p. 319.



sive deviation and also satisfy the demands for diathermy. Some manufacturers believed that this probably could be achieved but at a prohibitive cost. Others did not believe it could be done. Indeed, the manufacturers pointed out that diathermy equipment is operated by physicians and technicians who are not trained radio engineers and hence the users would not be in a position to make the necessary adjustments to maintain frequency stability as in radio broadcasting. Some manufacturers estimated that diathermy equipment which would meet the more rigid requirements would cost between \$1,000 and \$1,500, not to mention service expense. Naturally representatives of the medical profession voiced their objection to the increase in the cost of electromedical apparatus. The problem will have further study. A committee was appointed to look into engineering practices and circuit design costs and to report back to the group at a future conference.

#### PUBLIC HEALTH FELLOWSHIPS AVAILABLE TO QUALIFIED APPLICANTS FROM OTHER AMERICAN REPUBLICS

Pursuant to federal statutory authority, the Surgeon General of the United States Public Health Service has announced<sup>1</sup> that, to promote mutual aid and advancement in protecting the public health of the American republics and to bring about closer and more effective relationships between these republics, fellowships in the sciences related to public health are now available in the United States to qualified applicants from our sister republics. These fellowships will be awarded, after application through regular diplomatic channels, by the Surgeon General, on recommendation of the director of the Pan American Sanitary Bureau and with the approval of the Secretary of State of the United States. Applicants who qualify for selection for these fellowships must be (1) bona fide citizens of any one of the American republics other than the United States, (2) in good physical condition as evidenced by a certificate of medical examination issued by a physician within sixty days of the date of application, (3) able to speak, read, write and understand the English language and (4) of good moral character and possess intellectual ability and suitable personal qualities, and have successfully completed academic professional training in a recognized school in any one of the branches related to the science of public health, including, among others, medicine, dentistry, pharmacy, sanitary engineering, nursing, vital statistics, chemistry and bacteriology. These fellowships are to be of the training in research type. They may comprise (1) advanced scientific research in a recognized organization, university or other institution in the United States or (2) postgraduate work in an approved college or university, or internship and/or nonresident work in an approved hospital or other institution for the treatment, care or prevention of disease in the United States. The fellowships will be awarded for periods of varying length not exceeding one school year or twelve months of actual studies or research, but they may be extended on recom-

mendation of the director of the Pan American Sanitary Bureau. Successful applicants, on the recommendation of the director of the bureau, will be entitled to (1) reimbursement for necessary transportation expenses, (2) a per diem in lieu of subsistence allowance which shall not exceed \$5 a day while inside the United States and (3) other incidental expenses, including enrolment fees, tuition, medical and infirmary fees, laboratory fees, cost of textbooks and rental of equipment, payable to the institution, person or firm rendering or furnishing such services or supplies. The education of physicians and scientists from our sister American republics will do as much as any other project to earn for us friendship, respect and understanding. Even a small expenditure for such purposes may earn a vast return.

#### SAMPLE RACKETEERS

Just received is a copy of a letter written by one L. M. Wilson to a physician in Pennsylvania, suggesting that this physician write a letter to a dozen different manufacturers asking each of them to send him samples in large quantities to be used by his family. Apparently L. M. Wilson hopes some day soon to call on the doctor and to collect from him all these samples. Thus L. M. Wilson writes:

Dear Doctor: I am enclosing a list of a few items that I can buy from you and pay a fairly good price if you can obtain them. These items are all put out by large companies and will send this material indefinitely if not asked for too often i. e. once every month or 6 weeks. Will stop in to see you in about a month—as you should have them all by then if they are sent for immediately. Sample letter— Dear Sirs: I would like to request a supply of your product, —, —, for use in my own personal family—at your earliest convenience. Could you also enclose descriptive literature?

With this naive proposal is a list of all the different preparations to be requested, some apparently for use in the family, some for use by the doctor himself, as, for instance, for prostatic hypertrophy and for glandular stimulation, and others to be used in doing clinical research. Any physician who would cooperate in a performance of this type is participating in a distinctly unethical procedure and is lending himself to what is essentially a fraud.

#### PERIODICAL HONORS DR. HOWARD LILIENTHAL

The January-February issue of the *Journal of the Mount Sinai Hospital* is dedicated to Dr. Howard Lilienthal, the eminent surgeon, on the occasion of his eightieth birthday. In the foreword, written by Dr. Evarts A. Graham, it is pointed out that Dr. Lilienthal was one of the first to urge cholecystectomy as a more common operation than the then more used cholecystostomy. It was, however, the field of the thoracic cavity that called forth Lilienthal's most brilliant work. He published reports of the first considerable series of cases of lobectomy for bronchiectasis. His book *Thoracic Surgery*, published nearly twenty years ago, is still a classic. This number of the *Journal of the Mount Sinai Hospital*, dedicated by some seventy-five of Lilienthal's friends, associates and pupils, contains nearly fifty articles covering a wide range of medical subjects.

1. Federal Register 5: 5238 (Dec. 24) 1940.

## PHYSICAL DEFECTS AMONG DRAFTED MEN IN WORLD WAR

The United States Public Health Service has reanalyzed certain results of the medical findings pertaining to the prevalence of defects for the World War draft of 1917-1918.

Twenty-one per cent were rejected for military service, 31 per cent were classified as not available for general military service (including the rejections) and 52 per cent had one or more recorded defects.

These figures for the last war were summarized by Rollo H. Britten, senior statistician and George St. J. Perrott, chief, Division of Public Health Methods, Public Health Service (*Public Health Reports*, January 10).

"On the basis of the World War draft of 1917-1918, one might expect that, to meet the quota of 800,000

inducted men by July 1, 1941; 1,200,000 would have to be examined and thus that about 400,000 would not

### Defects per Thousand Total Drafted Men in 1917-1918

Orthopedic impairments .....	213.16
Eye defects .....	61.01
Cardiovascular-renal diseases .....	50.20
Underweight .....	31.14
Hernia and inguinal rings .....	55.36
Tuberculosis (all forms) actual or suspected .....	24.74
Defective or deficient teeth .....	26.27
Nervous or mental diseases .....	24.53
Ear defects .....	15.45
Veneral diseases .....	46.77
Varicose veins, varicocele .....	8.75
Gout .....	11.38
Hypertrophic tonsillitis .....	33.77
Arthritis and allied disorders .....	3.48
Asthma .....	2.33
Other diseases or defects .....	53.56
All diseases or defects .....	661.94

be available for general military service," the co-author stated.

## ARMY RESERVE OFFICERS ORDERED TO ACTIVE DUTY WAR DEPARTMENT

The following additional medical reserve corps officers had been ordered to active duty by direction of the War Department, Washington, D. C., up to January 10:

ALLISON, Ray Leonard, Captain, Los Angeles.  
ASHMAN, Philip, 1st Lieut., Vintondale, Pa.  
ABERNETHY, Lynn Dunlap, 1st Lieut., Holly Springs, Miss.  
COMSTOCK, Jack Arthur, 1st Lieut., Boulder, Colo.  
CUTTS, Francis William, 1st Lieut., Ventura, Calif.  
DICKSON, Douglas Dwight, 1st Lieut., Piedmont, Calif.  
FRENCH, Edward Brendan, 1st Lieut., Hyde Park, Vt.  
GORDON, Devitt Lawrence, 1st Lieut., Detroit.  
GROS, Hubert, 1st Lieut., Delphi, Ind.  
GUMINER, Stanley Herbert, 1st Lieut., Chicago.  
HARRIS, Sidney, 1st Lieut., Roselle, N. J.

KAPLAN, Louis, 1st Lieut., Philadelphia.  
McKEE, Claude Worth, 1st Lieut., Pittsburgh.  
MORGAN, Edward Shelley, 1st Lieut., Pendleton, Ore.  
ORR, Robert Alexander, 1st Lieut., Mayfield, Ky.  
PECK, Samuel Glen, 1st Lieut., Santa Ana, Calif.  
PLOTZ, Harry, Lieut. Col., Brooklyn.  
SHOENFELT, James Whitaker, Jr., 1st Lieut., Altoona, Pa.  
SMITH, George Yale, 1st Lieut., Brooklyn.  
ST. CLAIR, Alexander Armstrong, 1st Lieut., Bluefield, W. Va.  
SWITZER, Ralph Eugene, 1st Lieut., Haybro, Colo.

### Orders Revoked

Orders on the following officer reported in letter to this office dated Dec. 23, 1940, have been revoked:

AUSHERMAN, Howard Milton, 1st Lieut., Chattanooga, Tenn.

### FIRST CORPS AREA

The following additional medical reserve corps officers have been ordered to extended active duty with the regular army by the Commanding General, First Corps Area, since January 3. The First Corps Area comprises the states of Maine, Vermont, New Hampshire, Rhode Island, Massachusetts and Connecticut.

CHAMP, Anthony M., Major, Brockton, Mass., Fort Devens, Mass.  
BATCHELDER, Hollis G., Colonel, Dedham, Mass., Governor's Island, N. Y.  
BLOOMBERGH, John H., Lieut., Chestnut Hill, Mass., Camp Edwards, Falmouth, Mass.  
FOGG, Allston H., Major, Burlington, Vt., Camp Edwards, Falmouth, Mass.  
GURWITZ, Jack, 1st Lieut., Brookline, Mass., Camp Edwards, Falmouth, Mass.  
HALL, Leonard J., 1st Lieut., Lowell, Mass., Fort Devens, Mass.

MATTERA, Vincent J., 1st Lieut., Providence, R. I., Fort Devens, Mass.  
MENZIES, Gordon E., Captain, Wickford, R. I., Fort Adams, R. I.  
MORIARTY, Daniel J., 1st Lieut., Waitsfield, Vt., Fort Ethan Allen, Vt.  
SKRECKZO, Charles K., Lieut., Shelton, Conn., Carlisle Barracks, Pa.  
SPIRA, Bertram, Lieut., Worcester, Mass., Camp Edwards, Falmouth, Mass.  
TRASK, Burton W., 1st Lieut., Augusta, Maine, Camp Edwards, Falmouth, Mass.

### Orders Revoked

The following medical reserve corps officers have had their orders revoked:

DENNING, Walter S., 1st Lieut., Brookline, Mass.  
McIVER, Frederick D., Captain, Orleans, Vt.  
PHILLIPS, Robert T., Captain, Portland, Maine.  
ROZEN, Alan A., 1st Lieut., New Haven, Conn.  
SHAPIRO, Philip, 1st Lieut., Northampton, Mass.  
SIMARD, Louis B., 1st Lieut., Haverhill, Mass.  
WILLARD, Paul C., 1st Lieut., Montpelier, Vt.

### SECOND CORPS AREA

The following additional medical reserve corps officers had been ordered to active duty by the Commanding General, Second Corps Area, up to January 10, 1941. The Second Corps Area comprises the states of New York, New Jersey and Delaware.

ALBRECHT, Henry F., Jr., Captain, Troy, N. Y., Madison Barracks, N. Y., 1st Military Area.  
ALDEN, Carlos C., 1st Lieut., Buffalo, Fort Niagara, N. Y., 1st Military Area.  
AYER, Guy D., 1st Lieut., Cooperstown, N. Y., Fort Devens, Mass., 1st Military Area.  
BAYER, Eric, 1st Lieut., Englewood, N. J., Fort Ontario, N. Y., 3d Military Area.  
BEDRICK, John J., 1st Lieut., Bayonne, N. J., Fort Dix, N. J., 3d Military Area.  
BRUNDAGE, Frank E., Lieut. Col., Buffalo, Fort Niagara, N. Y., 1st Military Area.  
CATALANO, Russell J., 1st Lieut., Buffalo, Fort Niagara, N. Y., 1st Military Area.

CHIARULLI, Eugene E., 1st Lieut., Syracuse, N. Y., Fort Ontario, N. Y., 1st Military Area.  
CUNNINGHAM, Joel B., 1st Lieut., Camden, N. J., Fort Dix, N. J., 3d Military Area.  
DANFORTH, Edward P., Captain, Sidney, N. Y., Carlisle Barracks, Pa., 1st Military Area.  
DREIZIN, David H., 1st Lieut., Passaic, N. J., Carlisle Barracks, Pa., 3d Military Area.  
FIELDING, Robert T., 1st Lieut., Plainfield, N. J., State Armory, Newark, N. J., 3d Military Area.  
FISHER, Hyman B., 1st Lieut., New York, Fort Banks, Mass., 2d Military Area.  
FRANKEL, Henry, Captain, West New York, N. J., Fort Devens, Mass., 3d Military Area.  
FRATANUONO, M. J., 1st Lieut., Newark, N. J., State Armory, Newark, N. J., 3d Military Area.  
GOLDSMITH, Morris, 1st Lieut., Brooklyn, Camp Edwards, Mass., 2d Military Area.  
GOLDSTEIN, Sol R., Captain, Rochester, N. Y., Fort Ontario, N. Y., 1st Military Area.

GOODMAN, Kenneth, 1st Lieut., East Orange, N. J., Carlisle Barracks, Pa., 3d Military Area.  
GLADSTONE, Albert L., 1st Lieut., Paramus, N. J., Fort Dix, N. J., 3d Military Area.  
GREENFIELD, Herbert, 1st Lieut., Newark, N. J., Fort Dix, N. J., 3d Military Area.  
GUSTAFSON, Einar G., 1st Lieut., East Elmhurst, L. I., N. Y., Fort Hancock, N. J., 2d Military Area.  
HEMINWAY, Norman L., 1st Lieut., Somerville, N. J., Fort Williams, Maine, 3d Military Area.  
HOFFMAN, Sidney, 1st Lieut., Brooklyn, Fort Hamilton, N. Y., 2d Military Area.  
HOPKINS, Charles E. R., 1st Lieut., Brooklyn, Camp Upton, N. Y., 2d Military Area.  
INSABELLA, John, 1st Lieut., Newark, N. J., Carlisle Barracks, Pa., 3d Military Area.  
KNITZER, Carl, 1st Lieut., Brooklyn, Carlisle Barracks, Pa., 2d Military Area.  
KRAWCZYK, Joseph F., 1st Lieut., Buffalo, Fort Niagara, N. Y., 1st Military Area.  
Le BELL, Harold, 1st Lieut., New York, Carlisle Barracks, Pa., 2d Military Area.  
LINEHAN, Robert J., 1st Lieut., Binghamton, N. Y., Fort Ontario, N. Y., 1st Military Area.  
LIPSHUTZ, Daniel M., 1st Lieut., Brooklyn, Camp Upton, N. Y., 3d Military Area.  
LONG, Elias E., 1st Lieut., Long Branch, N. J., Fort Williams, Maine, 3d Military Area.  
LYNCH, Edward T., 1st Lieut., Elizabeth, N. J., State Armory, Newark, N. J., 3d Military Area.  
MASLANSKY, Lawrence, 1st Lieut., New York, Carlisle Barracks, Pa., 2d Military Area.  
McMAHON, Jeremiah J., 1st Lieut., Brooklyn, Governors Island, N. Y., 2d Military Area.  
MESSINA, Thomas, 1st Lieut., East Orange, N. J., State Armory, Newark, N. J., 3d Military Area.

#### FOURTH CORPS AREA

The following additional officers in the medical reserve corps have been ordered to active duty by the Commanding General of the Fourth Corps Area since January 3.

The Fourth Corps Area comprises the states of Tennessee, North Carolina, South Carolina, Alabama, Georgia, Mississippi, Florida and Louisiana.

HATCHER, Milford B., 1st Lieut., Macon, Ga., Fort McClellan, Ala.  
KEMP, Paul S., 1st Lieut., Macon, Ga., Fort McClellan, Ala.  
MATHIAS, Marion L., 1st Lieut., Charleston, S. C., Fort Bragg, N. C.  
MICHEL, Marshall L., 1st Lieut., New Orleans, Fort Bragg, N. C.  
PREVO, Samuel B., 1st Lieut., Memphis, Tenn., Fort Bragg, N. C.

#### SIXTH CORPS AREA

The following additional medical reserve corps officers had been ordered to extended active duty by the Commanding General, Sixth Corps Area, up to January 10. The Sixth Corps Area comprises the states of Michigan, Illinois and Wisconsin.

ABRAMS, Benjamin, 1st Lieut., Chicago, Reception Center, Fort Custer, Mich.  
BLUEFARB, Samuel M., 1st Lieut., Chicago Replacement Center, Camp Grant, Ill.  
BRENNER, Frank T., Captain, Cadillac, Mich., Puerto Rican Department.  
BROWN, Ira, Captain, Chicago, Station Hospital, Camp Grant, Ill.  
COUSENS, Marshall A., 1st Lieut., Chicago, Camp Grant, Ill.  
ENDRES, Fred C., Captain, Peoria Heights, Ill., Fort Knox, Ky.  
FARMER, David K., 1st Lieut., Broadlands, Ill., Fort Knox, Ky.  
FOX, William W., Captain, Lincoln, Ill., Fort Sheridan, Ill.  
FRIEDMAN, DAVID, Captain, Madison, Ill., 12th Cavalry, Fort Brown, Texas.  
GAZDA, Mace, 1st Lieut., Chicago, Fort Knox, Ky.  
GOODMAN, Paul P., 1st Lieut., Milwaukee, 5th Medical Battalion, Fort Knox, Ky.  
GORAN, Joseph R., 1st Lieut., Erie, Ill., Fort Knox, Ky.  
GORDON, Benjamin F., 1st Lieut., Newago, Mich., 5th Medical Battalion, Fort Knox, Ky.  
GORELICK, Harry S., 1st Lieut., Detroit, Station Hospital, Camp Grant, Ill.  
GRANDONE, Joseph J., Captain, Gillespie, Ill., Fort Sheridan, Ill.  
GREENSPAN, Gerald M., 1st Lieut., Chicago, 5th Medical Battalion, Fort Knox, Ky.  
GREER, Richard H., 1st Lieut., Northport, Mich., 1st Medical Square, Fort Bliss, Texas.  
HELM, Standiford, 1st Lieut., Evanston, Ill., Camp Livingston, La.  
HELMs, Jacob, Captain, Vanderbilt, Mich., Headquarters Fifth Army Corps.  
HURWITZ, Paul, 1st Lieut., Chicago, Station Hospital, Camp Grant, Ill.  
JACOBSON, Herman A., Captain, Chicago, Station Hospital, Camp Grant, Ill.  
KADIN, Maurice, 1st Lieut., Calumet, Mich., Station Hospital, Camp Grant, Ill.  
KATZ, Charles, 1st Lieut., Chicago, Station Hospital, Camp Grant, Ill.

MILLIGAN, Paul R., 1st Lieut., Orange, N. J., State Armory, Newark, N. J., 3d Military Area.  
O'BRIEN, John J., 1st Lieut., Flushing, N. Y., Fort Jay, N. Y., 2d Military Area.  
ORRIS, Harold J., Captain, Hill Side, N. J., Fort Monmouth, N. J., 3d Military Area.  
PARIS, William, 1st Lieut., Paterson, N. J., Fort Dupont, Del., 3d Military Area.  
PAYES, Leon J., 1st Lieut., Binghamton, N. Y., Fort Ontario, N. Y., 1st Military Area.  
PERROTTA, Anthony J., 1st Lieut., Red Bank, N. J., Fort Monmouth, N. J., 3d Military Area.  
PICCIOTTI, Joseph D., 1st Lieut., Rochester, N. Y., Fort Ontario, N. Y., 1st Military Area.  
ROMANO, Patrick J., 1st Lieut., Orange, N. J., State Armory, Newark, N. J., 3d Military Area.  
ROSS, Edward, 1st Lieut., Brooklyn, Fort Hancock, N. J., 2d Military Area.  
SAMUELS, Sol L., 1st Lieut., Plainfield, N. J., State Armory, Newark, N. J., 3d Military Area.  
SCHULTZ, Leo P., 1st Lieut., Jersey City, N. J., Carlisle Barracks, Pa., 3d Military Area.  
SIMPSON, David B., Captain, Bayonne, N. J., Fort Devens, Mass., 3d Military Area.  
SHANNON, William F., 1st Lieut., Bellmore, L. I., N. Y., Carlisle Barracks, Pa., 2d Military Area.  
STATMAN, Bernhard J., 1st Lieut., Newark, N. J., Carlisle Barracks, Pa., 3d Military Area.  
TIRRELL, Chester M., 1st Lieut., Orange, N. J., State Armory, Newark, N. J., 3d Military Area.  
VENET, Louis, 1st Lieut., New York, Fort Jay, N. Y., 2d Military Area.  
WOLEWITZ, Harry B., Major, Hackensack, N. J., Carlisle Barracks, Pa., 3d Military Area.  
ZUCKER, Isadore, 1st Lieut., Newark, N. J., Fort Dix, N. J., 3d Military Area.

#### Orders Revoked

The following officers previously reported have been relieved from duty or orders revoked:

BLEICH, Jack K., Captain, Atlanta, Ga.  
BUCKLEY, Madison H., 1st Lieut., Martin, Tenn.  
DE PRIEST, Frederick E., 1st Lieut., Coughatta, La.  
DE RAMUS, William H., 1st Lieut., Selma, Ala.  
FITZGERALD, Charles E., 1st Lieut., Farmville, N. C.  
GARY, Robert E., 1st Lieut., Tusculumbia, Ala.  
KAPLAN, Saul H., 1st Lieut., Miami Beach, Fla.  
LAIRD, Earl L., 1st Lieut., Union, Miss.  
SHAW, Clarence, 1st Lieut., Chattanooga, Tenn.  
TREHERNE, Alfred J., Captain, Atmore, Ala.

KERR, Charles R., Major, Chenoa, Ill., 4th Medical Supply Depot, Fort Sam Houston, Texas.  
KOEPP, Charles E., 1st Lieut., Marinette, Wis., Fort Knox, Ky.  
KUEHL, Frederick O., 1st Lieut., Green Bay, Wis., Fort Knox, Ky.  
LERNER, Harry A., 1st Lieut., Chicago, 50th Signal Battalion, Fort Sheridan, Ill.  
LANGE, Howard L., Captain, Belleville, Ill., Fort Knox, Ky.  
LANTING, Roelof, 1st Lieut., Gladwin, Mich., Camp Livingston, La.  
LEWIS, Robert M., 1st Lieut., Evanston, Ill., Reception Center, Fort Custer, Mich.  
LEWY, Robert B., Captain, Chicago, General Dispensary, U. S. Army, Chicago.  
MANTELL, Bernard, 1st Lieut., Chicago, 1st Medical Squadron, Fort Bliss, Texas.  
MARCUS, Daniel B., 1st Lieut., Detroit, Station Hospital, Camp Grant, Ill.  
McKINLEY, Hugh A., Captain, Highland Park, Ill., Station Hospital, Fort Sheridan, Ill.  
MELTZER, Herman L., Captain, Clinton, Ill., Station Hospital, Camp Grant, Ill.  
MILLIS, Jack W., 1st Lieut., Chicago, Reception Center, Fort Custer, Mich.  
O'FARRELL, Patrick F., Captain, Mount Olive, Ill., Fort Sheridan, Ill.  
OVITZ, John W., Jr., 1st Lieut., Sycamore, Ill., Station Hospital, Camp Grant, Ill.  
PHELPS, Gardner D., 1st Lieut., Chicago, Station Hospital, Camp Grant, Ill.  
RAND, George I., Captain, Chicago, Station Hospital, Camp Grant, Ill.  
RUBENSTEIN, Hyman I., Captain, Chicago, Fort Sheridan, Ill.  
REDMOND, Ralph N., 1st Lieut., Sterling, Ill., Station Hospital, Camp Grant, Ill.  
SAZAMA, Francis J., 1st Lieut., Berwyn, Ill., Fort Custer, Mich.  
SCHOWENGERDT, William H., Captain, Champaign, Ill., Camp Grant, Ill.  
SEXTON, George A., 1st Lieut., Monticello, Ill., Station Hospital, Camp Grant, Ill.  
STEIN, Morris F., Captain, Chicago, Station Hospital, Camp Grant, Ill.  
ST. PIERRE, Roderick G., Captain, Portland, Ore., Fort Sheridan, Ill.  
THRIFT, Chester B., Captain, Chicago, Fort Sheridan, Ill.  
WEICHSELBAUM, Paul K., 1st Lieut., Chicago, Station Hospital, Camp Grant, Ill.  
YOUNG, Joseph J., 1st Lieut., Appleton, Wis., Station Hospital, Camp Grant, Ill.

## MEDICAL LEGISLATION

## MEDICAL BILLS IN CONGRESS

*Bills Introduced.*—S. 27, introduced by Senator Caraway, Arkansas, proposes to authorize the refund of certain amounts collected from physicians between June 1, 1920 and June 30, 1931 for the privilege of prescribing the waters from Hot Springs National Park. S. 146, introduced by Senator White, Maine, proposes to grant pensions to male nurses who served under contract between April 21, 1898 and February 2, 1901. S. 286, introduced by Senator Sheppard, Texas, provides that the retired personnel of the Army, Navy, Marine Corps, and Coast Guard, and Fleet Naval and Fleet Marine Corps reservists requiring hospitalization shall be entitled to enter any Army or Navy hospital on their own personal request, under the same conditions as are now, or which hereafter may be fixed for the active service. H. R. 20, introduced by Representative Bland, Virginia, proposes to extend the benefits of the United States Employees' Compensation Act to employees of the Federal Civil Works Administration. H. R. 62, introduced by Representative Cannon, Missouri, proposes that all public laws granting medical and hospital treatment, domiciliary care, compensation and other allowances, pensions, disability allowance and retirement pay to veterans and dependents of veterans of the World War which were repealed in 1933 be reenacted. H. R. 84, introduced by Delegate Dimond, Alaska, contemplates the extension of the benefits of the United States Public Health Service to any person operating or employed on board certain vessels engaged in fishing operations. H. R. 98, introduced by Representative Dondero, Michigan, proposes to regulate the interstate transportation of containers of milk and other dairy products. H. R. 101, introduced by Representative Hull, and H. R. 1389, introduced by Representative Gehrmann, both of Wisconsin, propose to enact a "Dairy Products Stabilization Act" so as to provide for the promotion of sound dairy practices and to provide an adequate and balanced flow of milk and its products in interstate and foreign commerce. H. R. 124, introduced by Representative Cuklin, New York, proposes, among other things, that no person shall manufacture, import into the United States, transport in interstate or offer, sell or have in his possession for sale any oleomargarine, margarine, butterine or other substitutes for butter, manufactured wholly or in part from any fat other than that of milk or cream. H. R. 149, introduced by Representative Tenerowicz, Michigan, proposes a federal appropriation of \$250,000 to provide an addition to the Veterans' Administration hospital at Dearborn, Mich., to accommodate 250 patients. H. R. 156, introduced by Representative Voorhis, California, provides for the issuance by the Administrator of Veterans' Affairs of regulations providing for more liberal policies in determining the service connection of disabilities. H. R. 168, introduced by Representative Welch, California, provides for the construction of a marine tuberculosis hospital in California. H. R. 633, introduced by Representative Rogers, Massachusetts, provides that notwithstanding any provision of law or veterans' regulations, any World War ex-service man shown to have active tuberculosis of compensable degree shall be deemed to be totally disabled for purposes of compensation when hospitalized. H. R. 951, introduced by Representative Angell, Oregon, proposes a federal appropriation not to exceed \$2,500,000 to construct at Portland, Ore., a hospital for the care and treatment of the insane of the Territory of Alaska and of such other classes of persons who are insane or who may require mental treatment as the President may designate for care and treatment in the hospital. H. R. 958, introduced by Representative Angell, Oregon, and H. R. 1825, introduced by Representative Boland, Pennsylvania, propose an annual federal appropriation of \$11,580,000 to assist the states in the education of all children who are crippled, blind, partially seeing, deaf, hard of hearing, defective in speech, cardiopathic, tuberculous or otherwise physically handicapped and who for their education require an expenditure of money in excess of the cost of educating physically normal children. The administration of this bill will devolve on the Commissioner of Education. H. R. 960, introduced by Representative Angell,

Oregon, proposes to extend the benefits of the Social Security Act to include individuals who are physically disabled. H. R. 961, introduced by Representative Angell, Oregon, proposes to pay an annuity at a rate not to exceed \$50 per month to blind persons whose annual income is less than \$1,200, the term "blind person" being defined to mean a person who is 21 years of age or over and a citizen of the United States with not more than 20/20 of visual acuity in the better eye with maximum correction or whose field of vision is limited to 20 degrees or less from the fixation point in all quadrants. H. R. 995, introduced by Representative Patrick, Alabama, proposes to add a new title to the Social Security Act under which financial aid will be given to the states for the relief of the blind. The bill contemplates the furnishing of hospitalization, medical and surgical aid to needy blind individuals. H. R. 1008, introduced by Representative Rogers, Massachusetts, will, if enacted, provide prosthetic appliances to certain veterans suffering from non-service connected disabilities. H. R. 1022, introduced by Representative Geyer, California, proposes a federal appropriation not to exceed \$2,500,000 for the construction of a marine hospital at Los Angeles Harbor, Los Angeles. H. R. 1025, introduced by Representative Jenkins, Ohio, would authorize the payment of claims for unauthorized emergency treatment of disabled veterans in case no veterans' administration facilities are available. H. R. 1033, introduced by Representative Ludlow, Indiana, directs the Secretary of the Treasury to cause to be struck a medal of appropriate design with suitable emblems, devices and inscriptions, or a certificate suitable for framing, to commemorate the faithful nursing by the women who voluntarily offered their services and who served with the Army during the influenza epidemic of 1918. H. R. 1038, introduced by Representative Peterson, Georgia, provides for pensions to peacetime veterans of the regular Army, Navy, Marine Corps and Coast Guard suffering from arrested tuberculosis contracted while in the service. H. R. 1110, introduced by Representative Spence, Kentucky, proposes to create a Division of Water Pollution Control in the United States Public Health Service and to authorize the Division to prepare comprehensive plans for eliminating or reducing the pollution and improving the sanitary condition of the navigable waters of the United States and streams tributary thereto. The bill further proposes annual federal appropriations not to exceed \$50,000,000 to be available for grants-in-aid or loans to any state, municipality or other public body for the construction of necessary treatment works. H. R. 1391, introduced by Representative Gehrmann, Wisconsin, proposes to prohibit the importation of dairy products into the United States unless such products have been produced from milk or cream of cows which are either free from bovine tuberculosis and Bang's disease or which are under test for bovine tuberculosis and Bang's disease. H. R. 1395, introduced by Representative Green, and H. R. 2092, introduced by Representative Peterson, both of Florida, provide for the construction of a marine hospital in Florida. H. R. 1397, introduced by Representative Green, Florida, proposes a federal appropriation of \$2,500,000 for the construction of a marine hospital at Jacksonville, Fla. H. R. 1421, introduced by Representative Pace, Georgia, proposes a federal appropriation of \$2,500,000 for the construction of a veterans' hospital for the southwest section of Georgia, with a capacity of at least 800 beds. H. R. 1587, introduced by Representative Celler, New York, proposes, among other things, that whenever a veteran seeking service connection is shown to have been engaged in combat with the enemy, or to have been subjected to other conditions within the zone of advance, which can, in good medical judgment, be considered as causing or aggravating the disability or disabilities on which the claim is based, then the disability or disabilities shall be considered to have been caused or aggravated by military service. H. R. 1633, introduced by Representative Sheppard, California, proposes a federal appropriation of \$500,000 to construct a 200 bed veterans' hospital primarily for treatment of diseases of the chest, the hospital to be located in the Mojave Desert of either San Bernardino or Riverside County, Calif. H. R.

1798, introduced by Representative Sutphin, New Jersey, contemplates a complete survey of the physical education resources existing within the United States, such as outdoor recreative and competitive areas, gymnasiums, stadiums, swimming pools, and parks for the purpose of formulating a program to enable the youth of the nation to participate in supervised physical activities. H. R. 2082, introduced by Representative Flannery, and H. R. 2090, introduced by Representative Moser, both of Pennsylvania, propose to authorize the Secretary of the Interior to make certain inspections in coal mines to obtain information relative to health and safety conditions and occupational diseases. H. R. 2102, introduced by Representative Van Zandt, Pennsylvania, provides that in the administration of laws, regulations or rules by the United States Civil Service Commission there shall be no bar to the consideration of applications for employment under the federal government by World War veteran physicians or dentists by reason of time elapsing between graduation from medical schools of recognized standing and the date of application for examination or employment as physician or dentist. H. R. 2103, introduced by Representative Van Zandt, Pennsylvania, provides that any person who served in the military or naval forces of the United States during a recognized campaign or expedition, and who was honorably separated from such service, shall be granted hospitalization and domiciliary care by the Veterans' Administration subject to the same restrictions and limitations as are now applicable to World War veterans. H. R. 2105, introduced by Representative Van Zandt, Pennsylvania, would require the Administrator of Veterans' Affairs to amend the rating schedules so as to provide total ratings for the most severe functional nervous diseases or psychoneurotic states. H. R. 2108, introduced by Representative Vinson, Georgia, proposes to authorize the Secretary of the Navy to establish naval hospitals at the Naval Air Stations at Jacksonville, Fla., Corpus Christi, Texas, and San Juan, P. R.; the submarine base, Coco Solo, C. Z.; the naval station, Guantanamo Bay, Cuba, and the Marine barracks, Quantico, Va. H. R. 2112, introduced by Representative Vinson, Georgia, proposes to authorize the Secretary of the Navy to appoint in time of war or national emergency declared by the President to exist, for temporary service, such acting assistant surgeons as the exigencies of the service may require, who shall receive the compensation of assistant surgeons. S. J. Res. 10, introduced by Senator Sheppard, Texas, provides that enlisted men of the Army, Navy, Marine Corps and Coast Guard, when hospitalized or domiciled in either an army or navy hospital or the United States Soldiers' Home, shall be extended such treatment or domiciliary care without cost. S. 164, introduced by Senator Sheppard, Texas, and H. R. 2278, introduced by Representative May, Kentucky, propose to authorize the Secretary of War to detail not to exceed 2 per cent of the enlisted men of the regular army as students at such technical, professional and other educational institutions or as students, observers or investigators at such industrial plants, hospitals and other places as shall be best suited to enable such enlisted men to acquire a knowledge of or experience in the specialties in which it is deemed necessary that such enlisted men shall perfect themselves. S. 197, introduced by Senator Murray, Montana, proposes to amend the Selective Training and Service Act of 1940 so as to provide that any man selected for training and service under the act who has been awarded a degree of doctor of medicine or doctor of dental surgery by recognized medical or dental schools, who holds a valid license to practice medicine, surgery or dentistry in any state, territory or possession of the United States or the District of Columbia, and who is engaged in such practice at the time of his selection, and whose physical and mental fitness for such training and service has been satisfactorily determined shall, in lieu of induction for such training and service, be commissioned as an officer in the Medical Department Reserve, Officers' Reserve Corps, and ordered into active military service as provided by law. This bill further provides that medical and dental students at recognized medical and dental schools and interns and resident physicians, surgeons and dentists at recognized hospitals shall be exempt from training and service, but not from registration, under the act. Any such medical or dental student, intern or resident physician, surgeon or dentist, the bill further provides, who is a member of a reserve component of the land or naval

forces of the United States shall not be ordered or called to active duty or into active service in any of such forces without his consent, except in time of war. H. R. 549, introduced by Representative Merritt, New York, proposes a federal appropriation of \$1,875,000 to construct, at Whitehall, N. Y., or vicinity, a modern fireproof general medical-surgical veterans hospital and domiciliary facility, with a capacity of at least six hundred beds. H. R. 1007, introduced by Representative Rogers, Massachusetts, proposes a federal appropriation of \$2,300,000 for the first year of operation of the bill, and thereafter such sums as may be necessary, to enable the Public Health Service to assist states, counties, cities or other political subdivisions of the states to extend and improve measures through public and private institutions and organizations for the diagnosis, treatment and control of cancer, including the provision of hospital, diagnostic, clinic and other facilities for the diagnosis and treatment of persons suffering from cancer or suspected of suffering from this disease. H. R. 1074, introduced by Representative Schwert, New York, proposes to promote national preparedness and the national welfare through appropriation of funds to assist the several states and territories in making adequate provisions through schools for physical education, including athletics, instruction and guidance in healthful living, wider recreational use of school facilities and the development of school camps. H. R. 1425, introduced by Representative Peterson, Florida, proposes to authorize the Administrator of Veterans' Affairs to furnish outpatient treatment or medication, including pneumothorax therapy, insulin and liver extract, to honorably discharged veterans of the World War requiring such treatment or medication, notwithstanding that the disease necessitating the treatment or medication may not be directly or presumptively service connected. H. R. 1791, introduced by Representative Pfeifer, New York, proposes to establish a federal Department of Health. This department, it is proposed, will, among other activities, conduct researches, experiments and surveys, formulate and foster plans and compile and disseminate information for the purpose of promoting and maintaining health and sanitation. At the head of this department, it is proposed, will be a Secretary of Health, who must be a member of the medical profession. If the bill should be enacted, there will be transferred to the new department the Food and Drug Administration, the Division of Vital Statistics of the Bureau of the Census, Freedmen's Hospital and Saint Elizabeths Hospital, the Children's Bureau, and all functions of the United States Public Health Service, of the Bureau of Narcotics, and the Health Department of the District of Columbia.

## STATE MEDICAL LEGISLATION

### California

*Bills Introduced.*—S. 61, to amend the law relating to private institutions for insane and incompetent persons, proposes to impose an annual license fee on such institutions, the amount of which is to vary in accordance with the number of patients a particular institution is licensed to care for. For institutions licensed to receive not more than 20 patients, the fee proposed is \$5; for those licensed to receive more than 20 patients but not more than 25, the fee proposed is \$25; and for institutions licensed to receive more than 25 patients, the fee proposed is \$50. Under the present law the annual license fee is \$50 regardless of the number of patients for whom the institution is licensed to care. S. 130, to amend the use tax act, proposes to exempt from its provisions the storage, use or other consumption in the state of medicines and drugs used in the diagnosis, cure, mitigation, treatment or prevention of disease in man. Medicines and drugs, as so defined, are not to include any instrument or apparatus. A. 51 proposes to enact a new massage practice act and to vest the administration of that act in a state board of massage, to be appointed by the governor and to consist of three members who must have been actively engaged in the practice of massage for not less than three years preceding the date of their appointment. The bill proposes to define the practice of massage as "the use or employment of any method, art or science of administering to the human body for hygienic or therapeutic purposes exclusively, by rubbing, stroking, kneading, tapping or rolling the same manually, or the

external application or water, either natural or mineral to the human body, for the purpose of relieving or alleviating affected parts thereof." The bill proposes to exempt from its provisions persons duly licensed in the state to practice medicine, surgery, osteopathy, "drugless physician," [sic] chiropody or chiropractic and registered nurses while acting under the direct supervision of a "medical doctor." Certain present practitioners of massage, now residing in the state, are to be licensed without examination. Other applicants who are licensed to practice massage must furnish a satisfactory "testimonial" of good moral character and must furnish satisfactory evidence of graduation from a school or institution approved by the board. Apparently the board can approve only such an institution as requires a course of instruction of not less than thirty-four weeks, and a total number of hours for all courses of not less than one thousand hours as a condition precedent to graduation. A. 2, to amend the unemployment insurance act, proposes in effect to make unemployment insurance available to an employee who is unemployed because of illness and on whose behalf there is presented a certificate, signed by a licensed physician and surgeon, that the employee was unable to work during the period for which benefits were claimed because of illness.

#### Maryland

*Bills Introduced.*—H. 76 proposes that whenever the defendant in bastardy proceedings denies that he is the father of the child, and so petitions, the court shall order the complaint, the child and the defendant to submit to such blood tests as may be deemed necessary to determine whether or not the defendant can be excluded as being the father of the child. The result of the test is to be admissible in evidence only in cases in which definite exclusion is established. H. 34 proposes to authorize the Department of Public Welfare to establish two institutions for needy persons who require medical, nursing or custodial care by reason of chronic illness or infirmity.

#### Massachusetts

*Bills Introduced.*—H. 341 proposes that any town not maintaining or managing a hospital may annually appropriate not exceeding \$1,000 to a hospital established in such town or its vicinity for the establishment and maintenance of a free bed in the hospital for the care and treatment of persons who are residents of the town and unable to pay for necessary medical care and treatment. H. 215 proposes to require the operator of a motor vehicle involved in an accident, collision or violation of the automobile laws to report to the registrar of motor vehicles for a medical examination, the standards of which are to be made public from time to time. H. 272 proposes to appropriate \$25,000 to the board of registration in medicine to investigate and prosecute violations of the medical practice act and of the rules and regulations promulgated thereunder by the board.

#### Michigan

*Bills Introduced.*—S. 50 proposes to appropriate \$435,452.13 as a supplementary appropriation for the Michigan crippled children commission for the fiscal year ending June 30, 1941. S. 21 proposes to supplement former appropriations to the Michigan crippled children commission for the fiscal year ending June 30, 1941 in the following manner for the purposes stated: medical treatment of crippled children \$150,000; medical treatment of afflicted children \$300,000; unpaid bills and balance on prorated bills, medical treatment of crippled children \$78,788.61, and medical treatment of afflicted children \$356,663.52.

#### New York

*Bill Introduced.*—A. 167 proposes to permit physicians and nurses to disclose professional information acquired in attending a patient in a professional capacity where it appears that the patient has been the victim of professional negligence or incompetence which is the subject of a legislative investigation by the state or a political subdivision thereof.

#### Oklahoma

*Bills Introduced.*—S. 13 proposes that the committee on standardization of hospitals for crippled children shall consist of six members, one of whom must be a licensed dentist. H. 44 proposes to require food handlers to submit to physical examinations, including blood tests semiannually and to possess a certificate signed by the appropriate county health officer, showing they are free from syphilis, gonorrhea and tuberculosis.

#### Tennessee

*Bills Introduced.*—H. 102 authorizes the sexual sterilization of inmates of state institutions who are habitual criminals or are afflicted with hereditary forms of insanity that are recurrent, idiocy, imbecility, feeble-mindedness or epilepsy. H. 172 and S. 120, to amend the chiropractic practice act, proposes (1) to define chiropractic as the science of "palpating, analyzing and adjusting the articulations of the human spinal column and adjacent tissues by hand," (2) to condition the annual removal of a license on presentation of proof that the licensee has attended at least one of the semiannual sessions of the Tennessee Chiropractic Association during the year next preceding such application for renewal of license, and (3) to make eligible for examination for a license to practice any person who is a graduate of a school or college of chiropractic giving adequate courses in anatomy, physiology, bacteriology, pathology, chemistry, symptomatology, spinal analysis, hygiene, sanitation, principles and practice of chiropractic, and chiropractic philosophy, which school as a condition precedent to graduation required actual attendance of four school years of not less than nine months each.

## WOMAN'S AUXILIARY

#### Kentucky

The third midyear board meeting of the Woman's Auxiliary to the Kentucky State Medical Association was held at Louisville, November 12, with the president, Mrs. John M. Blades, Butler, presiding. Honored guests were the President of the Woman's Auxiliary to the American Medical Association, the president and president-elect of the Woman's Auxiliary to the Southern Medical Association and the president of the Kentucky State Medical Association. Dr. Austin Bell, Hopkinsville, president of the state association, outlined some objectives which the auxiliary might undertake.

#### Wisconsin

Mrs. Donne F. Gosin of Green Bay, president of the state auxiliary, spoke at the November meeting of the Fond du Lac County auxiliary, her subject being the "Aims of Our Organization." Mrs. Ernest S. Schmidt, state chairman of organization, also spoke. A talk on girl scouts was given by Mrs.

Claude Musolf of Fond du Lac. The Fond du Lac auxiliary sponsors a girl scout troop, donates money to the Children's Home and makes bandages for the Red Cross.

The Rock County auxiliary held its annual meeting, October 30, at Janesville with Mrs. H. E. Kasten of Beloit presiding. Annual reports of the Hygeia and philanthropic committees revealed that this group of thirty-five women had placed copies of *Hygeia* in homes, schools and libraries; had worked for the benefit of Mercy Hospital in Janesville and of Beloit Municipal Hospital, and had provided Christmas gifts and entertainment for all the patients at Pinehurst Sanitarium.

The Sauk County auxiliary, organized this year, met October 10 at Sauk City with Mrs. C. D. Pope presiding. The new project of this group is the making of layettes for use as needed by the doctors of the county.

The Sheboygan County auxiliary held its annual meeting, October 2, at Rocky Knoll Sanitarium, Plymouth. Mrs. A. J. Brickbauer is the new president.



## Medical News

(PHYSICIANS WILL CONFER A FAVOR BY SENDING FOR THIS DEPARTMENT ITEMS OF MORE OR LESS GENERAL INTEREST: SUCH AS RELATE TO SOCIETY ACTIVITIES, NEW HOSPITALS, EDUCATION AND PUBLIC HEALTH.)

ADDITIONAL MEDICAL COLLEGE NEWS AND ARTICLES APPEAR IN THE STUDENT SECTION, PAGE 339.

### ALABAMA

**Changes in Health Officers.**—Dr. Rutherford O. Ingham, Livingston, formerly health officer of Bibb County, has been assigned to a similar position in Limestone County. Dr. Robert W. Todd, New Orleans, has been appointed health officer of Russell County, succeeding Dr. Marion L. Shaddix, Phenix City, who recently was transferred to Clay County. Dr. Ralph H. Allen, formerly of Ruston, La., has been placed in charge of the health activities in Henry County. Dr. Bertha E. Stokes, Union Springs, has been appointed health officer of Bullock County, succeeding Dr. Delmer F. Parker, who resigned to enter the Indian Service of the U. S. Department of Interior, it is reported. Dr. Stokes will have her headquarters in Union Springs.

### CALIFORNIA

**Society News.**—The San Francisco County Medical Society was addressed January 14 by Dr. Walter C. Alvarez, Rochester, Minn., on "Abdominal Pain." A report on illness and hazards in automobile driving was submitted and discussed by Fred P. Williams, supervisor, California State Department of Motor Vehicles, division of drivers' licenses.

**New Cardiovascular Research Laboratory.**—A cardiovascular research laboratory will be opened at Mount Zion Hospital, San Francisco, January 31, under the direction of Dr. Meyer Friedman. A two day celebration will mark the opening, at which Dr. Louis N. Katz, Chicago, will present papers entitled "Role of Normal Kidney in Renal Hypertension" and "The Electrocardiogram in Coronary Disease," and Dr. Emanuel Libman, New York, "Pain" and "Libman-Sacks Disease."

**Health Defense Week.**—The week of February 2 to 9 has been designated "Health Defense Week" in Los Angeles. A resolution asking for a proclamation was presented to the mayor by a delegation of more than forty representatives of the Los Angeles County Medical Association, the woman's auxiliary, the junior section, the board of education, the University of California at Los Angeles, the College of Medical Evangelists, the health departments and other civic groups. The county society is planning to hold "The Los Angeles Health Defense Exposition" during the week at the Shrine Civic Auditorium ballroom.

**Midwinter Course on Ophthalmology and Otolaryngology.**—The Research Club of Los Angeles will open its tenth annual midwinter course in ophthalmology and otolaryngology at the Elks Club January 31. The program will include the following speakers:

- Dr. Edward Jackson, Denver, Methods of Measuring Refraction.
- Dr. Meyer Wiener, St. Louis, Surgery of the Globe.
- Russell L. Stimson, Los Angeles, Clinical Photography of the Eyes.
- Dr. Walter L. Lillie, Philadelphia, Some Practical Points Pertaining to the Routine Examination and Treatment of Patients in the Office.
- Dr. Roderic P. O'Connor, Oakland, Calif., Technique of the O'Connor Operation.
- Dr. Ralph I. Lloyd, Brooklyn, Perimetric Methods.
- Drs. John F. Barnhill, Miami Beach, Fla., and William J. Mellinger, Santa Barbara, Points in the Anatomy That Make Surgery of the Neck Comparatively Safe and Easy.
- Dr. Albert C. Furstenberg, Ann Arbor, Mich., Acute Infections of the Mouth and Pharynx.
- Dr. Gilbert Roy Owen, Los Angeles, Oto-Ophthalmologic Roentgenology.
- Dr. Isaac H. Jones, Los Angeles, Comments on Vitamins; Sense of Smell and Neuro-Otology.
- Drs. Leland G. Hunnicutt, Russell M. Decker, Pasadena, and Herman Z. Semenov, Beverly Hills, Changes in the Mucous Membranes Resulting from Growth, Disease and Drugs; Histopathologic Changes in the Nasopharynx and Eustachian Tubes in Relation to Chronic Catarrhal Deafness, and Histopathology of the Middle Ear and Sinuses; Allergy.

### CONNECTICUT

**Changes in Health Officers.**—Dr. Clarence G. Thompson, Norwich, has been appointed health officer of Ledyard. Dr. Kenneth L. Grevatt, Saybrook, has been appointed health officer of Redding, succeeding Dr. Albert J. Trimpert. Dr.

Edward P. Dunne has been named health officer of Unionville Borough, Unionville.

**Psychiatric Society Changes Name.**—The Connecticut Society for Psychiatry at a meeting in Hartford, December 11, voted to change its name to the Connecticut Society for Psychiatry and Neurology. Requirements for membership in the society were altered to make possible the admission of qualified neurologists.

**Society News.**—Dr. John S. Lockwood, Philadelphia, discussed "Progress Toward an Understanding of the Mode of Chemotherapeutic Action of the Sulfonamide Compounds" before the Yale Medical Society, New Haven, December 11. —The midwinter dinner of the Connecticut State Medical Society at the Lawn Club, New Haven, January 11, was addressed by Dr. Frank H. Lahey, Boston, President-Elect of the American Medical Association, on "Some Economic Problems by a Non-Professing Economist."

### DISTRICT OF COLUMBIA

**Course in Ocular Surgery, Pathology and Orthoptics.**—A special practical course in ocular surgery, pathology and orthoptics will be presented in Washington on April 14-18 by the resident staffs of the George Washington University School of Medicine and the Army Medical Museum. Additional information may be obtained from the Secretary, 927 Seventeenth Street N.W., Washington.

### ILLINOIS

**New Division of Social Hygiene.**—A division of social hygiene has been created in the state department of public health, the principal function of which will be to control the venereal diseases with especial emphasis on the eradication of syphilis. Dr. Herman M. Soloway, Chicago, has been made chief of the division.

**Society News.**—Dr. James E. Graham, Springfield, discussed "Varicose Veins" before the Madison County Medical Society in Edwardsville, January 3. —Dr. William Randolph Lovelace II, Rochester, Minn., discussed "The Use of Oxygen and Helium-Oxygen in Medicine and Surgery" before the Sangamon County Medical Society, Springfield, January 2. —Dr. Philip C. Jeans, Iowa City, discussed "Certain Aspects of the Nutrition of the Child" before the Rock Island County Medical Society in East Moline, January 14.

**Meeting of Bacteriologists.**—The winter meeting of the Society of Illinois Bacteriologists will be held at the Board of Trade Building, Chicago, January 31. Dinner will be followed by a program with four speakers, as follows:

- Mr. H. W. Cromwell, Abbott Laboratories, North Chicago, Experiences with Microbiologic Assay of Riboflavin (Vitamin G).
- Dr. Carl A. Dragstedt, Northwestern University Medical School, Chicago, Some Recent Studies in Anaphylaxis.
- John C. Garey, Ph.D., University of Illinois, Urbana, The Bacteriology of Brick Cheese.
- Dr. Wayne W. Fox, Northwestern University, Evanston, Laboratory Aids in Diagnosis and Treatment of Pneumonia.

### Chicago

**Professor Doisy Gives Steiglitz Lecture.**—Edward A. Doisy, Ph.D., professor and director of the department of biochemistry, St. Louis University School of Medicine, St. Louis, recently presented the first lecture under the Julius Steiglitz Memorial Lectureship at the University of Chicago. His subject was "Recent Developments in the Field of Vitamin K." The lectureship was established through joint effort of the Chicago section of the American Chemical Society and alumni of the department of chemistry of the University of Chicago.

**Joint Meeting on Otolaryngology.**—The middle section meeting of the American Laryngological, Rhinological and Otolological Society in a joint session with the Chicago Laryngological and Otolological Society will be addressed at the Drake Hotel, January 27, by the following:

- Dr. Harry C. Rosenberger, Cleveland, Herpetiform Inflammation of the Geniculate Ganglion with Facial Paralysis: A Subjective Experience.
- Dr. Samuel Iglauer, Cincinnati, Use of Preserved Human Cartilage in Reconstructive Facial Surgery.
- Melvin H. Knisely, Ph.D., Chicago, Dr. Warren K. Stratman-Thomas and Theodore S. Eliot, Ph.D., Memphis, Microscopic Observations of the Changes in the Blood and Circulation in Living Animals.
- Dr. William E. Grove, Milwaukee, An Evaluation of Ménière's Syndrome.
- Dr. James H. Maxwell, Ann Arbor, Mich., Some Experiences with Sinusitis in the Swimmer.
- Dr. Harold I. Lillie, Rochester, Minn., Suppurative Otitis Media, Acute Suppurative Labyrinthitis and Meningitis in a Pregnant Woman Near Term: Cesarean Section, Labyrinthectomy and Recovery.
- Stacy R. Guild, Ph.D., Baltimore, War Deafness and Its Prevention.

Capt. Cole D. Pittman, Chanute Field, Ill., Relation of High Altitude Flying and Rapid Changes of Atmospheric Pressure to Otolaryngology and Its Effect on the Middle Ear and Accessory Sinuses in Military Aviators.  
Dr. Paul H. Holinger, Chicago, Esophageal Perforations and Complications.  
Dr. John Mackenzie Brown, Los Angeles, president, was introduced at this meeting.

## INDIANA

**County Secretaries' Conference.**—The Indiana State Medical Association conducted its annual secretaries' conference at the Indianapolis Athletic Club, Indianapolis, January 19. Among the speakers were:

Leo X. Smith, Indianapolis, legal adviser, Indiana Township Trustees Association, and Dr. John S. Leffel, Connorsville, Administrative Problems in Care of the Indigent Sick.  
Dr. Louis W. Spolyar, Indianapolis, Problems of Health in Industry.  
Capt. Glen Ward, Indianapolis, The Medical Defense Program in Indiana.  
Dr. Robert A. Fargher, LaPorte, Attendance at County Society Meetings.  
Dr. Creighton Barker, New Haven, Conn., Everything Counts.  
Drs. Norman M. Beatty and Joseph William Wright, Indianapolis, Current Legislation.

Roundtable discussions were conducted on the following topics: What are county societies doing as to membership of men in military service?; types of membership; when and how to transact routine society business and membership of the colored physician.

## LOUISIANA

**Changes in Hospital Superintendents.**—Dr. Joseph O. Weilbaecher Jr. has been appointed acting director of Charity Hospital, New Orleans. He succeeds Dr. Roy W. Wright, resigned. Dr. Frank A. Donaldson, assistant superintendent of the Mississippi State Hospital, Whitfield, has been named superintendent of the East Louisiana Hospital for the Insane, Jackson. He succeeds Dr. Eugene M. Robards Jr., who became acting superintendent on the recent death of Dr. Charles S. Miller, who also served as acting superintendent. Dr. John T. Crebbin, Shreveport, has been elected superintendent of the Eye, Ear, Nose and Throat Hospital, New Orleans. Dr. Richard F. Gates, Hammond, was recently named superintendent of the Florida Parishes Charity Hospital, Independence.

**Society News.**—Recently elected officers of the Tri-State Medical Society of Texas, Louisiana and Arkansas, chosen at the meeting in Shreveport, include Drs. Rufus B. Robins, Camden, Ark., president; Spencer Allen Collom Jr., Texarkana, vice president from Texas; Robert T. Lucas, Shreveport, vice president from Louisiana; Joe F. Rushton, Magnolia, Texas, secretary-treasurer. The 1941 convention will be discussed "Hoarseness" before the LaFourche Valley Medical Society in Raceland, December 18. The Orleans Parish Medical Society was addressed in New Orleans, December 9, by Drs. Daniel N. Silverman and Robert A. Katz on "Plasma Therapy" and Idys Mims Gage, "Use of Plasma in Surgical Practice."

## MICHIGAN

**County Secretaries' Conference.**—The Michigan State Medical Society held its annual county secretaries' conference at Lansing, January 19. Dr. Horace Wray Porter, Jackson, chairman of secretaries, presided, and Dr. Harold W. Wiley, Lansing, president of the Ingham County Medical Society, delivered the address of welcome. The speakers included:

Dr. L. Fernald Foster, Bay City, The Future in Legislation.  
Dr. Henry R. Carstens, Detroit, Michigan Medical Service.  
Lieut. Col. Harold A. Furlong, Lansing, Medical Preparedness.  
H. Van Y. Caldwell, Cleveland, How to Make Your County Medical Society More Influential and Successful.  
The afternoon session was held in conjunction with a meeting of the state and county health officers and speakers were: Dr. Kenneth E. Markuson, Lansing, Industrial Health in Relation to National Defense.  
Dr. Wyman C. C. Cole, Detroit, Immunization Schedule.  
Dr. Arthur W. Newitt, Lansing, Tuberculosis Case Finding.  
Dr. Loren W. Shaffer, Detroit, New Five-Day Treatment for Syphilis.  
The honor guest at the noonday dinner was Lieut. Gov. Frank Murphy, who addressed the group on "Michigan's New Intangibles Tax Law."

## MINNESOTA

**Society News.**—At the December meeting of the Meeker County Medical Society in Litchfield, plans for the project for eradication of tuberculosis in the county were discussed by members of the committee on control of tuberculosis of the Minnesota State Medical Association, including Drs. Jay Arthur

Myers and Chester A. Stewart, Minneapolis; Edward A. Meyerding, St. Paul; Herbert A. Burns, Ah-gwah-ching, and Bertram S. Adams, Hibbing.

**Personal.**—Dr. Daniel C. Lohead, deputy city health officer of Rochester for sixteen years, has resigned, effective April 14. Dr. Floyd M. Feldman, director of rural health of district number 3 of the state board of health with headquarters in Rochester, has been appointed part time deputy, effective January 1. Dr. Karl H. Pfuetze, Nopeming, has been named superintendent of the Mineral Springs Sanatorium, Cannon Falls, succeeding Dr. William D. Beadie, who resigned because of ill health.

**Dr. Rous Will Present Christian Lecture.**—Dr. Francis Peyton Rous of the Rockefeller Institute for Medical Research will deliver the tenth annual George Chase Christian Lecture at the University of Minnesota Medical School, Minneapolis, February 5. His subject will be "Present Knowledge of Carcinogenesis." At a luncheon roundtable on the same day Dr. Rous will discuss "Latent Neoplastic Changes and Conditional Tumors." Tentative plans are being made for Dr. Rous to participate in a seminar on cancer to be arranged by Dr. Elexious T. Bell, Minneapolis, of the Cancer Institute Committee.

**Portrait of Dr. Litzenberg.**—A portrait of Dr. Jennings C. Litzenberg, Minneapolis, professor emeritus of obstetrics and gynecology, University of Minnesota Medical School, was unveiled at a dinner at the Minneapolis Club December 19 and presented to the university. Guy Stanton Ford, Ph.D., president of the university, received the gift. The portrait was painted by Edward Brewer of St. Paul. A native of Waubeck, Iowa, Dr. Litzenberg graduated at Minnesota in 1899. He joined the staff of his alma mater in 1907 as assistant professor of obstetrics. He was associate professor from 1910 to 1914, when he became professor and chief of the department. Dr. Litzenberg has served as president of the Hennepin County Medical Society, of the American Association of Obstetricians and Gynecologists and of the Minnesota Academy of Medicine, and has contributed extensively to the literature of his specialty. He became professor emeritus in 1938.

## NEW YORK

**Personal.**—Dr. Eric Ponder, director of the Biological Laboratory of the Long Island Biological Association at Cold Spring Harbor for the past five years, has resigned, and Millislav Demerec, Ph.D., of the department of genetics, Carnegie Institution of Washington, Cold Spring Harbor, was elected director for the year 1941. Mr. Arthur W. Page, president of the association, also resigned because of the pressure of other duties, and Robert Cushman Murphy, Sc.D., curator of oceanic birds at the American Museum of Natural History, was elected to succeed him.

**Society News.**—Dr. Benjamin J. Slater, Rochester, addressed the quarterly meeting of the Ontario County Medical Society in Canandaigua, January 14, on occupational diseases. Dr. Sydney W. Stringer addressed the Onondaga County Medical Society, Syracuse, January 7, on "Recent Advances in Sex Hormones." Dr. Ferdinand J. Schoenck, "The Effect of Smoking on Pregnancy." Dr. Richard B. Phillips, Rochester, Minn., addressed the Orleans County Medical Society, Albion, December 19, on "Recent Advances in the Dutchess County Psychiatric Society at a meeting of the Dutchess County Psychiatric Society at a meeting of the County of Nassau, Garden City, November 26, on "A New Maneuver for Shoulder Delivery."

## New York City

**Janeway Lecture at Mount Sinai.**—Dr. William B. Castle, professor of medicine, Harvard Medical School, Boston, delivered the Edward Gamaliel Janeway Lecture at Mount Sinai Hospital, January 24. Dr. Castle's subject was "Hemolytic Anemias."

**Fourth Harvey Lecture.**—Carl C. Speidel, Ph.D., professor of anatomy, University of Virginia Department of Medicine, Charlottesville, delivered the fourth Harvey Lecture of the current series at the New York Academy of Medicine, January 16. His subject was "Adjustments of Nerve Endings."

**Alumni Meeting Date Changed.**—The Annual Alumni Day at New York University College of Medicine will be held March 21 and 22 instead of on February 22 as in previous

years, it is announced. There will be a dinner the first evening and the following day will be devoted to a scientific program. There will be a luncheon Saturday, March 22, with Dr. Nathan B. Van Etten, President of the American Medical Association, as the guest speaker.

**Tuberculosis Hospital Opened.**—The new Triboro Tuberculosis Hospital in Jamaica, borough of Queens, was opened January 1. The new institution will serve principally the Bronx, Queens and Brooklyn. The building, which will ultimately care for 557 patients, is designed to provide a maximum of sunlight. On the patients' floors the outside walls have large areas of glass; the wards are separated by glass partitions and all open directly on balconies. The cost of the hospital was about \$3,500,000, of which 45 per cent was provided by a PWA grant. Dr. Alfred Ring is the superintendent.

### NORTH CAROLINA

**Seaboard Medical Association Meeting.**—Dr. Waverly R. Payne, Newport News, Va., was elected president of the Seaboard Medical Association at its forty-fifth annual meeting in Washington, December 3-5; Drs. George Erick Bell, Wilson, Wilbert E. Butler, Norfolk, Va., and Plummer A. Nicholson, Washington, were elected vice presidents, and Dr. Clarence Porter Jones, Newport News, Va., was reelected secretary. The speakers included:

- Dr. Norris W. Vaux, Philadelphia, The Maternal Pelvis in Relation to Labor.
- Dr. James P. Hennessy, New York, Uteroplacental Apoplexy.
- Dr. Julian L. Rawls, Norfolk, Va., The Response of Intrathoracic Tumors to Irradiation.
- Dr. Francis Bayard Carter, Durham, N. C., Mycotic Infection in Obstetric and Gynecologic Patients.
- Dr. Oscar Swineford Jr., Charlottesville, Va., Asthma and Heart Disease.
- Dr. Rachel D. Davis, Kinston, Intradermal Smallpox Vaccines.

**Appointments to Bowman Gray School of Medicine.**—The trustees of Wake Forest College recently announced the following appointments, among others, to the faculty of the new Bowman Gray School of Medicine of Wake Forest in Winston-Salem:

- Dr. James P. Rousseau, Winston-Salem, professor of radiology.
- Dr. John A. Rose, Philadelphia, associate professor of psychiatry.
- Dr. Frank R. Lock, New Orleans, associate professor of obstetrics and gynecology.
- Dr. Nelson M. Webster, Winston-Salem, assistant professor of obstetrics and gynecology.
- James Maxwell Little, M.S., Nashville, Tenn., assistant professor of physiology and pharmacology.

Dr. Rose will also be in charge of a child guidance clinic to be established under the sponsorship of the Junior League, the Winston-Salem Mental Hygiene Society and the new medical school. He has recently been on the staff of the Philadelphia Child Guidance Clinic and on the staff of the Institute for Mental Hygiene of the Pennsylvania Hospital.

### OHIO

**Annual Library Meeting.**—Dr. John F. Fulton, Sterling professor of physiology, Yale University School of Medicine, New Haven, Conn., was the guest speaker at the annual meeting of the Cleveland Medical Library Association, January 17. His subject was "The Life of Harvey Cushing."

**The Bunts Lecture.**—Lowell J. Reed, Ph.D., professor of biostatistics and dean, Johns Hopkins University School of Hygiene and Public Health, Baltimore, delivered the Frank E. Bunts Lecture at the Cleveland Clinic, January 8. His subject was "The Place of Statistical Method in Medical Science."

**Conference of Health Officers.**—The twenty-first annual conference of health commissioners of Ohio was held in Columbus, December 12-13. The speakers included Drs. Erval R. Coffey, U. S. Public Health Service, Washington, D. C., on "Environmental Sanitation"; Walter M. Simpson, Dayton, "Typhoid" and Ray S. Dixon, Detroit, "The Local Health Officer's Approach to the Control of Syphilis."

**Personal.**—Dr. Albert R. Smith, Iowa City, has been appointed orthopedist to the medical section of the state industrial commission, succeeding Dr. Clyde W. Dawson, Columbus, who resigned to enter private practice.—Dr. Eli R. Crew has resigned as superintendent of the Miami Valley Hospital, Dayton, after twenty-eight years in the position. His resignation will become effective when his successor is chosen, according to Hospitals.

### OKLAHOMA

**Lecture in Memory of Dr. Long.**—Dr. Ernest Sachs, professor of clinical neurologic surgery, Washington University School of Medicine, St. Louis, will deliver the first Leroy Long Memorial Lecture at the University of Oklahoma

School of Medicine, Oklahoma City, February 2. Dr. Sachs' subject will be "Surgery of Brain Tumors Today and Ten Years Ago." The lecture is sponsored by the Phi Beta Pi fraternity.

### WASHINGTON

**Society News.**—Dr. Marion M. Kalez addressed the Spokane County Medical Society, Spokane, December 12, on "Recent Advances in Aviation Medicine."—Dr. Christian R. Goodhope, Garfield, addressed the Whitman County Medical Society, January 9, in Colfax on heart disease.—Dr. Roger Anderson, Seattle, discussed treatment of sore and tender feet at a meeting of the Walla Walla Valley Medical Society, Walla Walla, December 12.

### GENERAL

**Special Society Elections.**—New officers of the Central Society for Clinical Research include Drs. Lawrence D. Thompson, St. Louis, president; Arlie R. Barnes, Rochester, Minn., vice president, and Carl V. Moore, St. Louis, secretary-treasurer. The society held its annual meeting on November 1-2 at the Drake Hotel in Chicago.—Dr. Richard S. Weiss, St. Louis, was chosen president of the American Academy of Dermatology and Syphilology at its annual meeting in Chicago, December 16. Other officers include Drs. John G. Downing, Boston, vice president; Earl D. Osborne, Buffalo, secretary and director, and Clyde L. Cummer, Cleveland, treasurer.

**Report of Foundation for Infantile Paralysis.**—The National Foundation for Infantile Paralysis, which derives its funds chiefly from the celebrations sponsored annually by the Committee for the Celebration of the President's Birthday on January 30, has issued its annual report. The National Foundation operates in two fields: the national field, in which it has so far acted principally as a grant-making agency, and the local field, through chapters now organized in more than 1,300 counties. The national activities cover five divisions: virus research, nutritional research, research on after-effects, epidemics and education. For studies on the virus the foundation has appropriated \$116,311.34 to various university and hospital investigators. A grant of \$37,500 was made to the University of Texas Faculty of Medicine, Galveston, for a study of the principles of nutrition and their application to the entire field of infectious diseases. It is believed that the broad approach is desirable in order that tools and methods of investigation may be developed before the specialized field is studied. Research on methods of reducing the impairment caused by infantile paralysis is being advanced by grants and appropriations totaling \$108,319.50. The work includes studies of hospital care, comparison of various methods of treatment and the entire problem of the manufacture and use of braces. The foundation's work in education includes not only dissemination of information to the public but provision for fellowships for young physicians, five for orthopedic surgeons and five for students of virus diseases. Grants have also been made for the training of orthopedic nurses and for establishment and expansion of courses to train them. A graduate school at the Georgia Warm Springs Foundation for the training of physical therapists is planned and lectures for physicians are in prospect. Pamphlets describing the use of respirators and "Toronto" splints, and one on nursing care of patients have been issued. For the educational activities grants and appropriations amounted to \$189,562.54. Epidemiologic studies were made during epidemics at Tacoma, Wash., and Detroit and in Indiana. In 1939 splints and frames were supplied to epidemic areas in New York and South Carolina and as a result the foundation has established a central supply depot in New York from which splints and frames have been shipped to all parts of the country. Recently a survey has been undertaken on the use of respirators. To carry out this work in epidemiology and epidemics, the foundation appropriated \$82,778.48. During the year ended Sept. 30, 1940, the foundation received a cash income of \$688,800.71, of which \$620,611.63 represented 50 per cent of the net proceeds of the 1940 Birthday Celebrations. The sixty-three grants and appropriations for the year amounted to \$709,471.68.

Local activities are financed by the remaining 50 per cent of the net proceeds of the Birthday Celebrations, which for the fiscal year ended Sept. 30, 1940, amounted to \$779,592.16. Under the supervision of the national organization the chapters give direct assistance to victims. During epidemics of last summer the chapters that were ready to meet the emergency gave splendid assistance not only to the victims but to the medical profession and the public health officers, the report said.

## Foreign Letters

### LONDON

(From Our Regular Correspondent)

Nov. 23, 1940 (delayed).

#### Treatment of War Burns

At the Royal Society of Medicine, Surgeon Rear Admiral Wakeley opened a discussion on the treatment of war burns. At the outbreak of war it was thought that the treatment would be simple, and the use of tannic acid was regarded as completely satisfactory. But this proved far from true in the navy, where many casualties from burns occurred. War burns differed from those of civilian life in that they might not be treated for many hours or even days. On a warship only first aid treatment could be given in the majority of cases. Most of the burns involved the face and hands and were due to gun flash, bomb flash, incendiary bombs or gasoline. First aid treatment consisted in morphine, warmth and fluid to counteract shock. If this was marked, plasma transfusion was given. Secondary shock occurred some hours after the burn and accounted for 80 per cent of the deaths. The most important factor in it was the loss of plasma from the burned surface. The blood might be so concentrated that the hemoglobin rose to 140 per cent. The best treatment was to replace the plasma protein. Given intravenously, plasma raised the osmotic pressure sufficient to restore the normal distribution of fluid between the vascular and interstitial components. Whole blood transfusion and intravenous physiologic solution of sodium chloride or sterile water were contraindicated. The amount of plasma necessary must be estimated by frequent blood examinations.

Wakeley agreed with Aldrich that acute toxemia from burns was due to streptococcal infection. It did not appear for several days and could be prevented by primary cleansing before coagulation. It was not nearly so common as in the last great war, for which no doubt coagulation was responsible. For extensive burns with toxemia, saline baths had proved valuable. In first or second degree burns, sepsis could be prevented if coagulation treatment was given at once and adequate cleansing and coagulation followed on arrival at a hospital.

With regard to local treatment, he favored gentian violet jelly with merthiolate (1:5,000), which could be applied to the burned areas without any cleansing. The application should be liberal, for it was painless and even soothing. It would seal off the burned area and formed a crust which remained until arrival at a hospital. Local treatment should not be given in the presence of shock. Tannic acid should not be used on the hands and face.

In the hospital the treatment of shock was instituted, and plasma banks and dried plasma were playing an important part. Oxygen administration was helpful. After shock had been treated the patient was taken to a warm room and anesthetized with gas and oxygen. The burned area was thoroughly cleansed with saline solution, dried with an electric hair drier and two applications of an aqueous solution of triple dye (2 per cent gentian violet, 1 per cent brilliant green and 0.1 per cent acriflavine) sprayed on the surface. This produced a thin, supple, adherent tan, which loosened about the eighth day and gradually fell off, leaving a healed area. If the burn was extensive and of third degree, the area should be excised and skin grafted.

Prof. W. C. Wilson said that coagulation treatment was used in secondary shock to minimize exudation, which it did. It also relieved pain. Whatever the cause of the acute toxemia, which was still unknown, it had become less common since coagulation treatment was instituted. Whether this was due to inhibition of bacterial growth was uncertain. Sepsis occurred predominantly in a deeply burned area, and the object of coagulation, which did not penetrate more than a millimeter of tissue,

was to make the conditions for bacterial growth as unsuitable as possible. This was done more effectively by coagulation than by any other form of local treatment.

Mr. A. H. McIndoe said that coagulation, so useful in preventing toxemia, had been carried too far, particularly when there was no evidence of toxemia. This held especially for tannic acid. In first or second degree burns, coagulation gave excellent results. But where the loss of skin was complete coagulation usually failed, particularly in regard to ultimate function. In these cases it was impossible to tan or coagulate the entire area. A heavily infected granulating surface was exposed in which healing might be slow and painful, and during this phase the patient might become wasted and anemic from chronic sepsis. Under the unyielding tannic acid, edema could develop to a degree which produced further deformity. In third degree cases treatment should be directed toward obtaining the best granulating surface for skin grafting. He showed slides illustrating the value of a thermostatically controlled saline bath, followed by saline packs and later by Thiersch grafts.

#### The Indispensable Corset

One of the measures of our war effort is the reduction of avoidable buying, such as of clothes, which the government enforces by reducing the quantity that wholesale dealers are allowed to supply to retailers. The object is to divert industry into war production as much as possible. But an order by the board of trade reducing the supply of corsets by half has brought trouble. The order was discussed by a meeting of press women at which no one agreed that corsets were a luxury. It was stated that 95 per cent of women out of their teens depend on a corset for support and comfort. A woman physician said that it was obvious that no woman was consulted in the matter. But the meeting seems to have ignored the point that the object of such orders is not to prevent the use of articles of attire but to promote economy by the wearing of old ones, which are often discarded for the sake of appearance—a thing which should be ignored to help the war effort.

#### Mosquitoes a War Danger

In the last great war precautions against the spread of malaria to England were found necessary because soldiers returned from malarial districts and were bitten by mosquitoes in this country. These mosquitoes became infected and thus spread the disease. As the same may occur in this war, the Ministry of Health has published a "Memorandum on Measures for the Control of Mosquito Nuisances in Great Britain," by Lieutenant Colonel Sinton and Mr. P. G. Shute. This memorandum gives a full account of the types of mosquito encountered in this country, of the reactions between mosquitoes and disease and of the measures to be taken to bring the mosquitoes under control.

## Marriages

JAMES WILLIAM WARD, Amarillo, Texas, to Miss Nancy Elizabeth Edwards of Nashville, Tenn., recently.

THEODORE WILLIAM WITALIS, Pomona, Calif., to Miss Betty Jane McPherson at Yuma, Ariz., Nov. 21, 1940.

JOHN H. ROBINSON III, Spartanburg, S. C., to Miss Betty Watson of Portsmouth, Va., in November 1940.

WILLIAM RICHARD SNELLING to Miss Julia Adella Meserve, both of Fernandina, Fla., in September 1940.

CLAUD WALTER PERRY JR. to Miss Marie Katherine Jenkins, both of Chattanooga, Tenn., Sept. 14, 1940.

THOMAS L. LAUDERDALE JR. to Miss Margaret Hornberger, both of Fort Worth, Texas, Nov. 20, 1940.

JAMES BISHOP BLODGETT, Detroit, to Miss Eleanor Fisher Clark of Bronxville, N. Y., Sept. 14, 1940.

## Deaths

**Paul Nicholas Leech, Ph.D.**, Director of the Division of Foods, Drugs and Physical Therapy in the headquarters office of the American Medical Association, died suddenly January 14 following a hemorrhage of the brain. He had suffered for some time with arterial hypertension. Dr. Leech was born in Oxford, Ohio, Aug. 12, 1889 and obtained his A.B. degree from Miami University, Oxford, Ohio, in 1910 and received the degree of master of science from the University of Chicago in 1911 and the Ph.D. in 1913. He also held the honorary degree of master of pharmacy from the Philadelphia College of Pharmacy. From 1911 to 1913 he was assistant in the Department of Chemistry at the University of Chicago, working with Prof. Julius Stieglitz. In 1913 he joined the staff of the American Medical Association as a chemist and in 1923 became director of the chemical laboratory, working under Prof. W. A. Puckner, who was the Secretary of the Council on Pharmacy and Chemistry. Following the death of Professor Puckner in 1932 Dr. Leech became Secretary of the Council on Pharmacy and Chemistry, and when the Board of Trustees created the Division of Foods, Drugs and Physical Therapy he was appointed director.

In 1918 Dr. Leech served as a lieutenant in the Sanitary Corps of the United States Army. He was a member of the American Chemical Society, a councilor from 1922 to 1936 and a director from 1928 to 1934. He also served as chairman of the Chicago section of the American Chemical Society in 1926. He was a member of the Chicago Chemists Club and trustee from 1925 to 1932. His contributions to medicine were recognized by associate fellowship in the American Medical Association and membership in the Institute of Medicine of Chicago. He was a member of Sigma Xi and an honorary member of Phi Beta Kappa. During his university career Dr. Leech contributed to research in the fields of formic acid, molecular rearrangements, medicinal chemistry and drug development. In his position as Secretary of the Council on Pharmacy and Chemistry, he served as an associate editor of many publications dealing with drugs, vitamins, glandular products and pharmacy. On several occasions he represented the American Medical Association in the United States Pharmacopoeial Convention. For more than a quarter of a century Dr. Leech rendered devoted service to the physicians of this country and earned for himself a nationwide reputation for integrity, scientific judgment and the highest ideals in the advancement of pharmacy and chemistry.

**Magnus A. Tate, Cincinnati**; Medical College of Ohio, Cincinnati, 1891; member of the Ohio State Medical Association; member of the House of Delegates of the American Medical Association from 1923 to 1928; formerly associate professor of clinical obstetrics, University of Cincinnati College of Medicine; past president of the Cincinnati Obstetrical Society and the Cincinnati Academy of Medicine; formerly vice president and secretary of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons; fellow of the American College of Surgeons; at various times on the staffs of Speer's Memorial Hospital, Dayton, Ky., Cincinnati General and St. Mary's Hospital; aged 72; died, Dec. 7, 1940.

**Allan Lockhart McLean, Halifax, N. S., Canada**; Dalhousie University Faculty of Medicine, Halifax, 1926; professor of epidemiology at his alma mater; at one time associate in preventive medicine, Medical College of Virginia,

Richmond; formerly health officer of Southampton County and Henrico County, Va.; at one time secretary of the Virginia Public Health Association; aged 44; died, Oct. 25, 1940.

**Charles Edward Duffin, Jeffersonville, Ind.**; Kentucky School of Medicine, Louisville, 1903; member of the Indiana State Medical Association; veteran of the Spanish-American and World wars; formerly served with the United States Public Health Service; at one time health officer of Richmond; aged 60; died, Nov. 21, 1940, in the Veterans Administration Facility, Marion.

**Hiram Bradbury Tebbetts, Los Angeles**; University of Southern California College of Medicine, Los Angeles, 1904; past president of the Los Angeles Obstetrical Society; served during the World War; formerly professor of physiology at the College of Dentistry, University of Southern California; for many years on the staff of St. Vincent's Hospital; aged 62; died, Nov. 26, 1940.

**George Otto Pobe** \* Port Jervis, N. Y.; Long Island College Hospital, Brooklyn, 1901; fellow of the American College of Surgeons; for many years health officer of Port Jervis and the town of Deer Park; aged 65; consulting surgeon to the Callicoon (N. Y.) Hospital; surgeon to the Deepark Hospital, where he died, Dec. 4, 1940, of arteriosclerosis.

**Edmund Waring Simons, Summerville, S. C.**; Medical College of the State of South Carolina, Charleston, 1905; member of the South Carolina Medical Association; served with the United States Public Health Service during the World War; for many years member of the school board; aged 73; died, Nov. 17, 1940.

**Jacob Tyree Woodson** \* West Hartford, Conn.; Columbia University College of Physicians and Surgeons, New York, 1920; served during the World War; on the staffs of the Hartford Hospital and the Municipal Hospital; aged 47; died, Nov. 9, 1940, of rheumatic heart disease and acute respiratory tract infection.

**Thomas Vincent Golden, Clarinda, Iowa**; John A. Creighton Medical College, Omaha, 1910; served during the World War; formerly health officer of Creston; on the staff of the Clarinda State Hospital; aged 53; died, Nov. 21, 1940, in the Veterans Administration Facility, Des Moines, of peritonitis.

**William Van Vorst Parramore, Cochran, Ga.**; University of Maryland School of Medicine, Baltimore, 1910; at one time medical superintendent of the State Tuberculosis Sanatorium, Alto; aged 56; was killed, Nov. 27, 1940, when the automobile in which he was driving was struck by a train.

**Joseph Egbert Pollard, Chatham, N. J.**; College of Physicians and Surgeons, medical department of Columbia College, New York, 1894; served during the World War; formerly associate medical director of the Prudential Insurance Company; aged 70; died, Nov. 29, 1940, in Clearwater, Fla.

**Charles Carlin Ayres, White Hall, Md.**; University of Maryland School of Medicine, Baltimore, 1914; member of the Medical and Chirurgical Faculty of Maryland; served during the World War; aged 48; died, Dec. 9, 1940, in the Maryland General Hospital, Baltimore, of cerebral hemorrhage.

**Corden Thorne Graham, Rochester, N. Y.**; University of Michigan Homeopathic Medical School, Ann Arbor, 1904; member of the Medical Society of the State of New York; served during the World War; aged 59; died, Nov. 26, 1940, in the Veterans Administration Facility, Batavia.

**Dorrance Ellsworth Sheffield, St. Johnsbury, Vt.**; University of Vermont College of Medicine, Burlington, 1923; member of the Vermont State Medical Society; served during the World War; aged 41; died, Nov. 24, 1940, in the Brightlook Hospital of coronary occlusion.

**Robert Cordner, Middletown, N. Y.**; Columbia University College of Physicians and Surgeons, New York, 1905; member of the Medical Society of the State of New York; at one time school physician; physician on the steamship *Panama*; aged 67; died in November 1940.

**Arthur Norman Clark, South Norwalk, Conn.**; College of Physicians and Surgeons, medical department of Columbia College, New York, 1883; aged 80; died, Nov. 25, 1940, in the Norwalk Hospital of carcinoma of the ascending colon with metastasis to the liver.

**George Davis Vick, Selma, N. C.**; Jefferson Medical College of Philadelphia, 1906; member of the Medical Society of the State of North Carolina; member of the school board; aged 63; died, Nov. 2, 1940, of coronary occlusion, hypertension and arteriosclerosis.



PAUL NICHOLAS LEECH, PH.D.  
1889-1941

**Will Foster Fyke**, Springfield, Tenn.; Vanderbilt University School of Medicine, Nashville, 1918; member of the Tennessee State Medical Association; secretary of the Robertson County Medical Society; aged 50; died, Nov. 27, 1940, of cardiorenal disease.

**Ira Raymond Willits** Ⓢ Chicago; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1905; aged 58; died, Dec. 3, 1940, in St. Mary's Hospital, Galesburg, Ill., of hypertensive heart disease and chronic nephritis.

**Theodore B. Fulper**, Hampton, N. J.; Jefferson Medical College of Philadelphia, 1889; member of the Medical Society of New Jersey; formerly medical inspector for the schools and a member of the board of health; aged 73; died, Nov. 15, 1940, of uremia.

**Louis Harward Webb**, Sunmount, N. Y.; Jefferson Medical College of Philadelphia, 1910; served during the World War; served with the Veterans Administration for many years; manager of the Veterans Administration Facility; aged 52; died, Nov. 12, 1940.

**Henry Russell Hitchcock**, Plymouth, Mass.; Harvard Medical School, Boston, 1890; member of the Massachusetts Medical Society; formerly served with the United States Public Health Service; aged 79; died, Nov. 23, 1940, of cerebral hemorrhage.

**Charles Lawrence Weiher**, Poughkeepsie, N. Y.; Bellevue Hospital Medical College, New York, 1885; member of the Medical Society of the State of New York; aged 81; died, Nov. 18, 1940, in the Vassar Brothers Hospital of angina pectoris.

**John Henry Rose** Ⓢ Kansas City, Kan.; University of Kansas School of Medicine, Kansas City, 1906; for many years police surgeon; aged 63; died, Nov. 26, 1940, in St. Margaret's Hospital of pneumonia after an operation for appendicitis.

**Clifford Dennison Hamrick** Ⓢ Passed Assistant Surgeon Lieutenant, United States Navy, San Diego, Calif.; Emory University School of Medicine, Atlanta, Ga., 1930; entered the navy in 1930; aged 40; died, Nov. 27, 1940, of pneumonia.

**Earle J. Brashear**, North Pleasureville, Ky.; Hospital College of Medicine, Louisville, 1898; aged 65; died, Nov. 27, 1940, in the Pewee Valley Sanitarium and Hospital, Pewee Valley, of bleeding peptic ulcer with secondary anemia.

**Charles Frederick Voigt** Ⓢ Midway, Ky.; University of Louisville (Ky.) Medical Department, 1915; past president and secretary of the Woodford County Medical Society; served during the World War; aged 47; died, Nov. 19, 1940.

**Benjamin Wise Burt**, Holly Springs, N. C.; College of Physicians and Surgeons, Baltimore, 1886; member of the Medical Society of the State of North Carolina; aged 78; died, Nov. 14, 1940, of arteriosclerotic heart disease.

**Francis David John Chippendale**, Fall River, Mass.; Georgetown University School of Medicine, Washington, D. C., 1936; member of the Massachusetts Medical Society; aged 28; died, Nov. 19, 1940, of subacute endocarditis.

**Karl L. Thorsgaard** Ⓢ Chicago; Rush Medical College, Chicago, 1900; served in various capacities on the staffs of the Augustana Hospital and the American Hospital; aged 65; died, Nov. 24, 1940, of coronary thrombosis.

**Henri Gedeon Coupal**, Montreal, Que., Canada; M.B., School of Medicine and Surgery of Montreal, Faculty of Medicine of the University of Laval at Montreal, 1908, and M.D. in 1910; aged 55; died, Nov. 2, 1940.

**Thomas Hightower Hancock**, Atlanta, Ga.; College of Physicians and Surgeons, medical department of Columbia College, New York, 1891; member of the Medical Association of Georgia; aged 71; died, Nov. 17, 1940.

**Leon Clifford Wills**, Philadelphia; Jefferson Medical College of Philadelphia, 1907; member of the Medical Society of the State of Pennsylvania; aged 58; died, Nov. 10, 1940, of cerebral thrombosis and arteriosclerosis.

**Henry Claiborne McCullough** Ⓢ Town Creek, Ala.; Medical College of Alabama, Mobile, 1905; president of the Lawrence County Medical Society; aged 63; died, Nov. 8, 1940, of carcinoma of the parotid gland.

**Clarence Curtin Bobb** Ⓢ Lykens, Pa.; Temple University School of Medicine, Philadelphia, 1919; served during the World War; aged 45; died, Nov. 16, 1940, in St. Joseph Hospital, Reading, of coronary occlusion.

**Charles Merritt Ausley**, Tallahassee, Fla.; Baltimore Medical College, 1901; for many years member of the board of county commissioners; aged 61; died, Nov. 22, 1940, of bronchopneumonia and arthritis.

**Virgil Eugene Franklin**, Graymont, Ga.; University of Maryland School of Medicine, Baltimore, 1896; member of the Medical Association of Georgia; aged 70; died, Nov. 13, 1940, of cerebral hemorrhage.

**Frank Alvin Rogers**, Boston; Medical School of Maine, Portland, 1876; member of the Massachusetts Medical Society; formerly health officer and school physician in Everett; aged 85; died, Nov. 15, 1940.

**Thomas J. Fleming** Ⓢ Philadelphia; University of Pennsylvania Department of Medicine, Philadelphia, 1894; on the staff of St. Joseph's Hospital; aged 68; died, Nov. 23, 1940, of coronary thrombosis.

**Edward James O'Rourke** Ⓢ Cambridge, Mass.; Tufts College Medical School, Boston, 1909; on the staff of the Cambridge City Hospital; aged 54; died, Nov. 20, 1940, of coronary heart disease.

**Walter Clarence Friday**, Starkville, Miss.; Memphis (Tenn.), Hospital Medical College, 1913; served during the World War; aged 49; died, Nov. 15, 1940, of bilateral pulmonary tuberculosis.

**Clyde Edward Cox** Ⓢ Worcester, Mass.; Harvard Medical School, Boston, 1930; on the staffs of the City Hospital and the Fairlawn Hospital; aged 35; died, Nov. 10, 1940, of acute coronary occlusion.

**Terry Augustus Walter**, Portland, Maine; Hahnemann Medical College and Hospital of Philadelphia, 1914; served during the World War; aged 59; died, Nov. 23, 1940, of coronary occlusion.

**William Harrison Floyd** Ⓢ Jena, La.; Memphis (Tenn.) Hospital Medical College, 1910; aged 55; died, Nov. 21, 1940, in the Baptist Hospital, Alexandria, of carcinoma of the head of the pancreas.

**Jennie Elizabeth Mabee**, Poughkeepsie, N. Y.; Cornell University Medical College, New York, 1923; member of the Medical Society of the State of New York; aged 43; died, Nov. 7, 1940.

**D. Ross Hinton**, Start, La.; University of Tennessee College of Medicine, Memphis, 1914; aged 53; died, Nov. 23, 1940, in a hospital at Monroe of acute rheumatic fever and influenza.

**Jesse Lee Cook**, Oxford Junction, Iowa; Keokuk (Iowa) Medical College, College of Physicians and Surgeons, 1900; aged 64; died, Nov. 2, 1940, in Cedar Rapids of diabetes mellitus.

**Thomas A. Irwin**, Franklin, Pa.; Chicago Homeopathic Medical College, 1888; member of the Medical Society of the State of Pennsylvania; aged 78; died, Dec. 5, 1940, of heart disease.

**Egbert Frederick Henderson**, Edmonton, Alta., Canada; McGill University Faculty of Medicine, Montreal, Que., 1921; served during the World War; aged 49; died, Oct. 29, 1940.

**Leo Strousse**, Philadelphia; Jefferson Medical College of Philadelphia, 1906; on the staff of the Jewish Hospital; aged 55; died, Nov. 30, 1940, of chronic myocarditis and nephritis.

**Paul B. Waldman**, Reading, Pa.; Hahnemann Medical College and Hospital of Philadelphia, 1884; aged 82; was found dead, Nov. 19, 1940, of heart disease.

**Andrew J. Cook**, Flora, Ind.; Eclectic Medical Institute, Cincinnati, 1884; aged 81; died, Nov. 19, 1940, of cerebral hemorrhage and arteriosclerosis.

**Frank Virgil Willard**, Loveland, Colo.; University of Colorado School of Medicine, Denver, 1938; aged 29; died in November 1940 of meningitis.

**Cora E. Alcorn**, Spokane, Wash.; Central Medical College of St. Joseph, Mo., 1900; aged 68; died, Nov. 29, 1940, of carcinoma of the breast.

**Eugene Warren**, East Cleveland, Ohio; Chicago Homeopathic Medical College, 1894; aged 70; died, Nov. 11, 1940, of cerebral hemorrhage.

**James L. Gray**, Chicago; Hering Medical College, Chicago, 1907; aged 82; died, Nov. 29, 1940, in St. Bernard's Hospital of tetanus.

**Joseph J. Rosenberg**, New York; University and Bellevue Hospital Medical College, New York, 1903; aged 59; died, Nov. 6, 1940.



## Correspondence

### USE OF POWDERED CRYSTALLINE SULFANILAMIDE IN SURGERY

*To the Editor:*—In the Nov. 16, 1940 issue of *THE JOURNAL*, the local use of sulfanilamide is discussed in an editorial. Reference was made of its use in solution as a direct irrigation of the wound in cases of combined abdominoperineal or posterior resection of the rectum. During the past year at the Roosevelt Hospital we have been using the powdered crystalline sulfanilamide directly in the peritoneal cavity at the time of operation.

On Jan. 10, 1940 I used the crystalline drug locally in the peritoneal cavity in a critical case of diffuse peritonitis due to a ruptured appendix. Shortly after the recovery of this patient, its local peritoneal use became routine at Roosevelt Hospital in cases of abdominal infection and it was used also prophylactically in certain types of intestinal resection. To date 175 patients have been treated in this manner with excellent results. Of the 175 cases of all kinds, 55 were those of abscess and peritonitis following ruptured appendixes; 8 of the cases of peritonitis were considered to be of the diffuse variety and the condition at, or before, operation was considered to be critical. Deaths did not occur in this group of 55 cases.

The group of cases in which drainage was done was remarkable for the rapidity with which drained wounds healed. The complications developing postoperatively in this group of 55 cases were few: three abscesses of the abdominal wall; one case of pyelitis; two fecal fistulas, both of which healed before discharge from the hospital, and four mild respiratory complications.

The average time before discharge in these cases was twenty days. The patients ranged in age from 4 months to 72 years.

For use in the operating room, the drug is placed in cork-stoppered test tubes in amounts of 2, 4, 6 and 8 Gm. It is then sterilized by dry heat for one-half hour at 120 C. The drug should not be autoclaved.

The powdered drug is placed in the peritoneal cavity just before the peritoneal layer is sutured or, in cases of abscess just before the drains are inserted. The amount used varied; in adults from 10 to 12 Gm. was the average used. The amount varied with the weight of the patient and the severity of the peritoneal infection. We have used as much as from 16 to 18 Gm. in severe conditions. Infants received from 2 to 4 Gm. One fourth the total amount is reserved for the layers of the abdominal wall during complete or partial closure of the wound.

Blood levels of the sulfanilamide reach a high level as soon as two hours after operation in cases in which drainage is not done. The peak of the blood level is reached in twelve hours and falls at the end of thirty-six hours. In cases in which drainage is done, the levels are usually slightly lower. The average blood level has been 7 mg. per hundred cubic centimeters of blood.

However, the blood level is of secondary importance, as the local level of the drug in the peritoneal exudate of from 200 to 300 mg. has a direct effect which cannot be produced in any other way. In 20 per cent of the cases the blood level was maintained postoperatively, the drug being given orally, rectally or by hypodermoclysis after the second day and continued for five or six days more.

Our results with the sulfanilamide at Roosevelt Hospital have been so consistently good in cases of severe peritoneal infection that we have not tried sulfathiazole powder, although we have used the latter elsewhere locally with good results.

R. STERLING MUELLER, M.D., New York.

### CHANGES IN PLASMA VOLUME

*To the Editor:*—In studying the behavior of the plasma volume during diuresis it is apparent that changes in the plasma volume will depend for their magnitude on the intensity of the diuresis in proportion to the volume of the plasma. To illustrate the superiority of the edematous dog to the edematous cardiac patient for experimental purposes in this respect, I give the following approximate average values taken from the recently published paper of Swigert and Fitz (*THE JOURNAL*, Nov. 23, 1940, p. 1786) and the papers of Bryan, Evans, Fulton and Stead (*Arch. Int. Med.* 55:735 [May] 1935) and Evans and Gibson (*Am. J. Physiol.* 118:251 [Feb.] 1937):

	Plasma Volume	Urine Flow Before Salyrgan	Maximum Urine Flow After Salyrgan	Increase
Edematous cardiac patient	3,000 cc.	1.8 cc./min.	5.8 cc./min.	3.1 ×
Edematous dog.....	1,000 cc.	0.6 cc./min.	8.3 cc./min.	14 ×

It may be inferred that trebling the flow of urine when the plasma volume is 3,000 cc. may place no burden on the equilibrium between the tissue fluids and the blood, whereas increasing the flow of urine fourteen fold and to a higher rate with a plasma volume of only 1,000 cc. would affect that equilibrium and produce demonstrable and consistent changes in the plasma volume.

The changes observed by Swigert and Fitz are not consistent, as they concede, and do not on the whole exceed the limits of biologic variation and experimental error, so that it does not seem reasonable to ascribe them to the diuresis induced by salyrgan.

WILLIAM A. EVANS JR., M.D., Detroit.

### AMPUTATIONS

*To the Editor:*—I have been following with interest the articles of the Council on Physical Therapy on "Amputations." Certain statements in Chapter III call for comment, since they would leave the inexperienced surgeon with a totally erroneous impression of the value of end bearing amputations. As we are again faced with the prospect of many amputations from war injuries it is of extreme importance that the experience of the past war be placed on record.

It cannot be too strongly emphasized that end bearing amputations (Syme and Stokes-Gritti) are greatly superior to all other forms of amputation in the lower extremity. The amount of weight which must be borne on a lower extremity stump is so great that only skin which is naturally adapted to weight bearing can be expected to stand the stress during a lifetime of usage. Amputations through the middle of the tibia in which the weight is taken on hairy skin against the oblique expanded end of the tibia are at a great physiologic disadvantage. This results in frequent complications due to hair follicle infections in the weight bearing area, painful indurations as well as the vascular disturbance known as "choked stump," which results in a boggy edematous end to the stump, which fissures and permits infection to enter. Of the below knee amputations through the tibia which were performed on Canadian soldiers of the last war a large proportion have been reamputated and converted into Stokes-Gritti amputations to the entire satisfaction of the patient, the surgeon and the limb maker.

Syme's amputation provides a stable, painless stump which never gives trouble because of the amount of weight it is called on to bear. The technic of the operation is not unduly difficult. The sole step of outstanding importance is to retain a good blood supply to the heel flap. It is better than Pirogoff's amputation, since it allows more space beneath the stump for the ankle joint mechanism of the artificial leg and because it avoids

the possibility of complications due to failure of the fragment of the calcaneus to unite by bone to the tibia. It is quite possible to make a very satisfactory artificial leg for Syme's amputation with an ankle joint mechanism in it, and excellent ones are being made by Canadian limb makers. It is true that it must be strong because of the leverage strains it must bear, and this means metal reinforcing, which means a moderately heavy limb. But even this feature has been overcome by the use of aluminum alloys, so that in the best types of limbs, such as the Dew limb, the weight does not exceed 3 pounds. The appearance means nothing in a male patient, for the limb is entirely concealed by his clothing. For women, by more elaborate craftsmanship, it can be made so inconspicuous as to be scarcely noticed. One of my Syme's amputations is in a young woman whose artificial limb is so much less noticeable than was her deformed extremity with its apparatus that her life has been completely transformed.

Functionally Syme's amputation is easily the best of all the amputations of the lower extremity. It permits weight bearing without any restrictions. The patient can be on his feet all day and work at heavy occupations. The gait is natural. The artificial limb is easy to fit and gives little trouble. Its only complications are due to misplacement of the weight bearing flap or undue looseness of the flap. These features, if necessary, can be corrected by secondary plastic operations. In my experience circulatory complications never occur in it. Compared with the midtibial amputation its advantages are so great that it should always be performed if possible. No midtibial amputation permits walking all day or the performance of heavy work, whereas this is common experience with Syme's amputation.

Stokes-Gritti's amputation above the knee has the same merits that Syme's amputation has below the knee. It permits full weight bearing on the end of the stump without any complications due to the weight bearing. The technic is slightly more difficult. It is essential that the patella be firmly fused to the femur without tilt or lateral displacement. If this is attained, a good functional stump is assured on which the patient can walk all day without disability from weight bearing. So useful is this amputation that it has been used to replace many below-knee stumps of poor weight bearing function. The loss of voluntary knee joint action has proved of less consequence than ability to stand and walk without periods of disablement due to damage to the skin from weight bearing.

It is a great mistake to condemn out of hand Syme and Stokes-Gritti amputations or to damn them with faint praise. Beyond doubt they are the best amputations of the lower extremity. It is a source of amazement to me that the British Ministry of Pensions in its recent brochure should condemn these weight bearing stumps. I can attribute its experience only to poor limb making. During the last war the Canadian government established its own limb factory, which was and still is an integral part of the soldier's hospital at Christie Street in Toronto. This resulted in direct control of the process of artificial limb making by the surgeons who dealt with amputations and with end bearing stumps and the artificial limbs that are fitted to them. There commonly is but little correlation between the surgeon and the artificial limb maker. It is a mistake, however, to say that satisfactory limbs cannot be made for Syme or Stokes-Gritti amputations. Some ingenuity may be needed but the problem is susceptible of satisfactory solution.

The problem of amputations is of such importance and is likely to be of so much more importance in the immediate future that I have found it impossible to refrain from comment on your important series of articles and especially on the subject of end bearing stumps in the lower extremity.

R. I. HARRIS, M.C., M.B., F.R.C.S.(C.), Toronto.  
Associate Professor of Surgery, University  
of Toronto Faculty of Medicine.

Medical Examinations and Licensure

COMING EXAMINATIONS

BOARDS OF MEDICAL EXAMINERS  
BOARDS OF EXAMINERS IN THE BASIC SCIENCES  
Examinations of boards of medical examiners and boards of examiners in the basic sciences were published in THE JOURNAL, January 18, page 248.

NATIONAL BOARD OF MEDICAL EXAMINERS  
NATIONAL BOARD OF MEDICAL EXAMINERS: Parts I and II. Various centers, February 10-12. Exec. Sec., Mr. Everett S. Elwood, 225 S. 15th St., Philadelphia.

EXAMINING BOARDS IN SPECIALTIES  
AMERICAN BOARD OF ANESTHESIOLOGY: Oral. Part II, Cleveland, May 31-June 1. Final date for filing application is April 1. Sec., Dr. Paul M. Wood, 745 Fifth Ave., New York.  
AMERICAN BOARD OF INTERNAL MEDICINE: Oral. April, in advance of the meeting of the American College of Physicians and June, in advance of the meeting of the American Medical Association. Written. Oct. 20. Final date for filing application is Sept. 1. Sec., Dr. William S. Middleton, 1301 University Ave., Madison, Wis.  
AMERICAN BOARD OF NEUROLOGICAL SURGERY: Written. Philadelphia, June 6-7. Sec., Dr. R. Glen Spurling, 404 Brown Bldg., Louisville, Ky.  
AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY: Part II, Groups A and B, Cleveland, May 28-June 1. Final date for filing application is March 15. Sec., Dr. Paul Titus, 1015 Highland Bldg., Pittsburgh.  
AMERICAN BOARD OF OPHTHALMOLOGY: Oral. Cleveland, May or June. Sec., Dr. John Green, 6830 Waterman Ave., St. Louis.  
AMERICAN BOARD OF PATHOLOGY: Oral and Written. Cleveland, June 2-3. Final date for filing application is May 1. Sec., Dr. F. W. Hartman, Henry Ford Hospital, Detroit.  
AMERICAN BOARD OF PEDIATRICS: Chicago, May 18, following the Region III meeting of the American Academy of Pediatrics. Boston, Oct. 12, immediately following the annual meeting of the American Academy of Pediatrics. Sec., Dr. C. A. Aldrich, 723 Elm St., Winnetka, Ill.  
AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: Oral. Washington, May 2-3. Final date for filing application is Feb. 22. Sec., Dr. Walter Freeman, 1028 Connecticut Ave., N.W., Washington, D. C.  
AMERICAN BOARD OF RADIOLOGY: Oral. Cleveland, May 30-June 1. Final date for filing application is April 15. Sec., Dr. Byrl R. Kirklin, 102-110 Second Ave., S.W., Rochester, Minn.  
AMERICAN BOARD OF SURGERY: Part II. San Francisco, Feb. 3. Written. Part I. Various centers, April 2. Sec., Dr. J. Stewart Rodman, 225 South Fifteenth St., Philadelphia.

South Dakota July Report

Dr. J. F. D. Cook, director, South Dakota Board of Medical Examiners, reports the written examination for medical licensure held at Rapid City, July 16-17, 1940. The examination covered 13 subjects and included 100 questions. An average of 75 per cent was required to pass. Three candidates were examined, all of whom passed. Five physicians were licensed to practice medicine by reciprocity and 1 physician so licensed by endorsement. The following schools were represented:

School	PASSED	Year Grad.	Per Cent
Northwestern University Medical School.....	(1940)	86	87.1
University of Wisconsin Medical School.....	(1939)		85.9
School	LICENSED BY RECIPROCITY	Year Grad.	Reciprocity with
Northwestern University Medical School.....	(1937)		Michigan
State University of Iowa College of Medicine.....	(1927)		Minnesota
Detroit College of Medicine and Surgery.....	(1922)		Michigan
University of Minnesota Medical School.....	(1938)		Minnesota
University of Pennsylvania School of Medicine.....	(1936)		Minnesota
School	LICENSED BY ENDORSEMENT	Year Grad.	Endorsement of
Rush Medical College.....	(1937)	N. B. M. Ex.	

Hawaii July Report

Dr. James A. Morgan, secretary, Board of Medical Examiners, Territory of Hawaii, reports the oral and written examination for medical licensure held at Honolulu, July 8-11, 1940. The examination covered 10 subjects and included 80 questions. An average of 75 per cent was required to pass. Seven candidates were examined, all of whom passed. The following schools were represented:

School	PASSED	Year Grad.	Per Cent
University of Colorado School of Medicine.....	(1939)		84.1
Northwestern University Medical School.....	(1939)		79.1
Tulane University of Louisiana School of Medicine.....	(1937)		79
Harvard Medical School.....	(1937)		86.4

Columbia University College of Physicians and Surgeons	(1898)	78.4
Long Island College Hospital	(1914)	81.5
Ohio State University College of Medicine	(1938)	81

Five physicians were licensed to practice medicine by endorsement from February 19 through August 26. The following schools were represented:

School	LICENSED BY ENDORSEMENT	Year Endorsement Grad. of
Northwestern University Medical School	(1939)	N. B. M. Ex.
Indiana University School of Medicine	(1936)	N. B. M. Ex.
University of Louisville School of Medicine	(1936)	N. B. M. Ex.
Tulane Univ. of Louisiana School of Medicine	(1936), (1938)	N. B. M. Ex.

### Virginia June Report

Dr. J. W. Preston, secretary, Board of Medical Examiners of Virginia, reports the written examination for medical licensure held at Richmond, June 18-20, 1940. The examination covered 8 subjects and included 80 questions. An average of 75 per cent was required to pass. One hundred and thirty candidates were examined, 129 of whom passed and 1 failed. The following schools were represented:

School	PASSED	Year Grad.	Per Cent
George Washington Univ. School of Med.	(1939) 77, 87,	(1940)	84, 85
Georgetown University School of Medicine	(1940)		83
Howard Univ. College of Medicine	(1939) 81, 83,	(1940) 80,	81, 88
University of Minnesota Medical School	(1940)		80
Johns Hopkins University School of Medicine	(1940)		84
New York Medical College, Flower and Fifth Avenue Hospitals	(1939)		81
Duke University School of Medicine	(1938)		77
Jefferson Medical College of Philadelphia	(1940)		84
Medical College of Virginia	(1939)		85,
88, (1940) 75, 78, 79, 80, 80, 81, 81, 81, 81, 81,			
82, 82, 82, 82, 82, 83, 83, 83, 83, 83, 84, 84,			
84, 84, 84, 85, 85, 85, 85, 85, 85, 85, 85, 86,			
86, 86, 86, 87, 88, 88, 88, 89			
University of Virginia Department of Medicine	(1938)		80,
(1940) 77, 79, 79, 79, 79, 79, 80, 80, 80, 80, 81,			
81, 81, 81, 81, 81, 81, 82, 82, 82, 82, 82, 82, 82,			
82, 82, 82, 82, 82, 83, 83, 83, 83, 83, 83, 83,			
83, 83, 84, 84, 84, 84, 84, 85, 85, 85, 85, 85, 86,			
86, 86, 86, 87, 88, 88, 88, 89			
University of Wisconsin Medical School	(1938)		84
Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin	(1931)		75
Vereinigten-Friedrichs-Universität Medizinische Fakultät, Halle Wittenberg	(1920)		84
University of Edinburgh Faculty of Medicine	(1934)		81*
School	FAILED	Year Grad.	Number Failed
Université de Genève Faculté de Médecine	(1936)		1

Twenty-five physicians were licensed to practice medicine by reciprocity and 10 physicians so licensed by endorsement from February 27 through July 12. The following schools were represented:

School	LICENSED BY RECIPROCITY	Year Grad.	Reciprocity with
College of Medical Evangelists	(1932)		California
George Washington University School of Medicine	(1927), (1932), (1934), (1938)		
Georgetown University School of Medicine	(1933), (1937)		Dist. Colum.
Johns Hopkins University School of Medicine	(1935), (1937)		Maryland
Washington University School of Medicine	(1938)		Missouri
Cornell University Medical College	(1936)		New York
University of Buffalo School of Medicine	(1923)		New York
Ohio State University College of Medicine	(1936)		Ohio
University of Cincinnati College of Medicine	(1938)		Ohio
Jefferson Medical College of Philadelphia	(1927)		Dist. Colum.
Meharry Medical College	(1938), (1939)		Tennessee
University of Tennessee College of Medicine	(1933), (1939)		Tennessee
University of Tennessee Medical Department	(1901)		Montana
Vanderbilt University School of Medicine	(1938)		Tennessee
University of Virginia Department of Medicine	(1936)		Louisiana
Licentiate of the Royal College of Physicians of London and Member of the Royal College of Surgeons of England	(1926)		Maryland
Université de Montpellier Faculté de Médecine	(1932)		Penna.

School	LICENSED BY ENDORSEMENT	Year Endorsement Grad. of
College of Medical Evangelists	(1938)	N. B. M. Ex.
Georgetown University School of Medicine	(1937)	N. B. M. Ex.
Northwestern University Medical School	(1937)	U. S. Navy
Tufts College Medical School	(1936)	N. B. M. Ex.
Albany Medical College	(1938)	N. B. M. Ex.
Duke University School of Medicine	(1937)	N. B. M. Ex.
Medical College of the State of South Carolina	(1932)	N. B. M. Ex.
Meharry Medical College	(1937)	N. B. M. Ex.
Medical College of Virginia	(1937, 2)	N. B. M. Ex.

\* License has not been issued.

## Bureau of Legal Medicine and Legislation

### MEDICOLEGAL ABSTRACTS

**Medical Practice Acts: Injunction to Enjoin Disciplinary Proceedings by Licensing Agency Denied.**—The defendant Missouri State Board of Health, the state medical licensing agency, commenced disciplinary proceedings against the plaintiff physician, charging that he had been convicted of using the mails to defraud, had engaged in a prohibitive type of advertising relative to diseases of the sexual organs and had been guilty of other unprofessional and dishonorable conduct. In the manner prescribed by law the secretary of the board notified the plaintiff to appear at the hearing that was to be held before the board. Instead of appearing before that board and answering the charges made, the plaintiff filed a petition with the circuit court, St. Louis County, division 3, for an injunction to restrain the board from proceeding on its charges, alleging a subsequent pardon for the conviction and that the other charges did not constitute unprofessional conduct. The board demurred to the plaintiff's petition on the ground that the petition alleged insufficient facts to entitle the plaintiff to any relief, that the circuit court had no original jurisdiction in the premises and that under the laws of Missouri the state board of health had exclusive initial jurisdiction in revocation proceedings. From an order overruling its demurrer and granting the injunction, the defendant board appealed to the Supreme Court of Missouri, division 1.

The defendant contended that it was acting within its exclusive jurisdiction when it maintained proceedings to determine whether or not a license to practice medicine should be revoked and that the plaintiff was not entitled to an injunction restraining such proceedings because, if he felt aggrieved by the board's decision, he could have appealed to the circuit court by a writ of certiorari. The Supreme Court said that in general a court of equity will not interfere by injunction for the purpose of controlling the acts of public officers constituting inferior tribunals—such as supervisors, commissioners of highways and the like—on matters properly pertaining to their jurisdiction since the proper remedy was a review at law by writ of certiorari. The court therefore held that, since the defendant board was functioning lawfully within its exclusive initial jurisdiction, the plaintiff was not entitled to an injunction to restrain the board from proceeding to take disciplinary action against him. Judgment for the plaintiff was therefore reversed, and the preliminary restraining order was dissolved.—*Hughes v. State Board of Health*, 137 S. W. (2d) 523 (Mo., 1940).

### Malpractice: Alleged Failure Timely to Recognize and Advise Patient as to Nonunion of Fracture of Tibia.

—The plaintiff suffered on April 1 a spiral fracture of the tibia and a "rough" transverse fracture of the fibula, about opposite each other at the junction of the lower and middle third of those bones. He was hospitalized and the physician defendant reduced the fractures and applied a splint that day. A plaster cast was applied and roentgenograms were taken the following day. The patient was discharged from the hospital April 3 and was told to remain in bed for about thirty days, which he did, the defendant visiting him once in the interim. The patient returned to the defendant June 2. The physician, after taking another roentgenogram and opening the cast by splitting it lengthwise, informed the patient that the leg was "fine" and that a good callus was forming. The patient complained at that time that the leg was sore and painful. The physician "put part of the cast back" and advised the patient to use crutches. The patient returned late in June, complaining that his leg was still sore and painful, and the physician applied heat by an electric pad and again told the patient that the "break" was "coming fine" and that the callus was getting stronger. During early July the physician again saw the patient and took a third

roentgenogram. The leg at that time was "wobbly," it "sagged in the center" and was "turning out." The physician still advised that the leg was "coming along fine" and that a good callus was forming. The use of crutches was continued until late July when a cane was utilized. The plaintiff was never able to put his full weight on his left leg. On September 17 he again called at the physician's office, complaining that his leg was more pliable than ever and "that it was just like he had an extra joint between the knee and the ankle." The physician then made a fluoroscopic examination. About two weeks later the patient went to a clinic in a nearby town and was informed, apparently, that there was nonunion and that an operation would be necessary to effect a union. The patient told the defendant physician of this advice and on the defendant's suggestion Dr. Fortin, a "bone specialist" of Fargo, N. D., was put in charge of the case. The defendant accompanied the patient to Fargo the following day and a day later Dr. Fortin operated and found that the fibula had united but that there was nonunion of the tibia. He sawed off the ends of the fragments of the tibia and inserted between them a bone graft. What the end result was the published report of the case does not state. Subsequently the patient brought suit for malpractice against the defendant physician, and from a judgment in favor of the patient the physician appealed to the Supreme Court of North Dakota.

The complaint filed alleged that the physician breached his duty to his patient in that three months after assuming the care of the patient, and at times thereafter, he informed the patient that the leg was coming along all right and was in good condition and that the fracture had been properly reduced and was healing, and thereby deceived the patient into continuing under his care and treatment when the physician should have known, if proper regular and careful examination and treatment had been given, that the broken limb had not united and never had been properly reduced. The sole question before the Supreme Court was whether or not the evidence adduced at the trial was sufficient to justify a verdict and judgment for the patient. The only expert testimony, aside from that of the defendant, was that of Dr. Fortin who testified on behalf of the defendant, in effect, that the early treatment rendered by the defendant, including the application of the cast and instructions that the patient remain in bed for thirty days, was proper, that the cast should be permitted to remain on from six to eight weeks and that it then was proper to remove the cast to make an examination of the progress of healing. This witness examined the roentgenograms taken by the defendant on April 2, June 2 and July 5. With regard to the roentgenogram taken on June 2, he testified that it showed little callus; that it would be proper treatment at that time to immobilize the leg longer and instruct the patient to walk around with the aid of crutches, bearing some weight on the injured leg. The roentgenograms taken on July 5, he stated, indicated that nature had not thrown down callus in the process of healing the fractured tibia, although the fibula appeared to be united. At the time of the third roentgenogram, he further testified, "We know we have a delayed union or coming to a non union" and "There is no set course for that"; one might apply another cast or a splint, or one might operate and put in new bone and attempt to make nature throw down callus. He stated on cross examination, however, that by the time the third roentgenogram had been taken, that is, on July 5, three months after the injury, if no union had been effected, "the chances of getting bony union thereafter, except by operation, is wholly speculative . . . most of the time."

It is the duty of a physician, said the Supreme Court of North Dakota, citing 48 C. J. 1133, to act with the utmost good faith toward his patient, and if he knows that he cannot accomplish a cure or that the treatment adopted will probably be of no benefit, it is his duty to advise his patient of these facts, and if he fails to do so he is guilty of a breach of that duty. The evidence in the present case, continued the court, entirely justified the conclusion that the defendant deceived the patient both in July and in September, and at times in between, when he told him that the leg was coming along fine and that everything was all right. According to Dr. Fortin, the fracture was a very severe one and was located in an area where nonunion, if treated

according to the methods which the defendant had utilized, was not at all unlikely, and he must have known in July and in September that there was no union and that union was unlikely. Notwithstanding this, he did not inform the plaintiff of the seriousness of the situation. He in fact misrepresented the true situation to the patient. Nor did he inform his patient that another method of treatment, by operation, was accessible within easy reach. According to the evidence the defendant recognized at once, when informed of the patient's consultation with the clinic, that the situation required the services of a "bone specialist." The duty of a physician to his patient is measured by conditions as they exist and not by what they have been in the past or may be in the future. Today, with the rapid methods of transportation and easy means of communication, the horizon has been widened and the duty of a physician is not fulfilled merely by utilizing the means at hand in the particular village where he is practicing. So far as medical treatment is concerned, the borders of the locality and community have, in effect, been extended so as to include those centers readily accessible where appropriate treatment may be had which the local physician, because of limited facilities or training, is unable to give. The defendant not only failed to inform his patient as to the true condition of the broken bones as shown by the roentgenograms but made inaccurate and misleading statements concerning the same—statements that naturally would lead the patient to believe that the condition of his injured leg was wholly satisfactory and that the broken bones apparently were forming a proper and satisfactory union when the truth was that the roentgenogram showed only a "little callus present" and "a delayed union or coming to a non union." The defendant continued a treatment which, in the plaintiff's case at that time, was "conjectural and speculative," and he failed to inform the plaintiff that there was another method of treatment, namely surgery, available in a not distant city which was more likely to result in a union of the broken bones than the treatment that was being given. In the judgment of the court the evidence was sufficient to warrant the jury in finding that the defendant failed to perform the duty which he owed to the plaintiff and that, because of such failure, the plaintiff suffered detriment. If the defendant, on July 5, had informed the plaintiff of the true condition of the broken bone, as shown by the roentgenogram taken that day, and had further informed him as to the method of treatment that was most likely to effect a union of the broken bones, the plaintiff could and probably would have obtained such treatment some three months earlier than he did and thus have been spared at least three months of expense, pain and suffering.

Accordingly, the judgment in favor of the patient was affirmed. There was, however, a strong dissenting opinion by two justices who differed with the majority opinion as to the conclusions to be drawn from the testimony adduced.—*Tvedt v. Hauge*, 294 N. W. 183 (N. D., 1940).

## Society Proceedings

### COMING MEETINGS

Annual Congress on Medical Education and Licensure, Chicago, Feb. 17-18. Dr. W. D. Cutter, 535 North Dearborn St., Chicago, Secretary.

American Orthopsychiatric Association, New York, Feb. 20-22. Dr. Norville C. La Mar, 149 East 73d Street, New York, Secretary.

Central Surgical Association, Ann Arbor, Mich., Feb. 28-March 1. Dr. George M. Curtis, Ohio State University, Columbus, Ohio, Secretary.

Middle Section, American Laryngological, Rhinological and Otological Society, Chicago, Jan. 27. Dr. Walter H. Theobald, 307 North Michigan Blvd., Chicago, Chairman.

Mid-South Post Graduate Medical Assembly, Memphis, Tenn., Feb. 11-14. Dr. A. F. Cooper, Goodwyn Institute Bldg., Memphis, Tenn., Secretary.

Pacific Coast Surgical Association, Los Angeles, Feb. 19-22. Dr. H. Glenn Bell, University of California Hospital, San Francisco, Secretary.

Society of Surgeons of New Jersey, Newark, Jan. 29. Dr. Walter B. Mount, 21 Plymouth St., Montclair, Secretary.

Society of University Surgeons, St. Louis, Feb. 14-15. Dr. Frank Glenn, 525 East 68th St., New York, Secretary.

Western Section, American Laryngological, Rhinological and Otological Society, San Francisco, Feb. 1-2. Dr. Robert C. Martin, 384 Post St., San Francisco, Chairman.

## Current Medical Literature

### AMERICAN

The Association library lends periodicals to members of the Association and to individual subscribers in continental United States and Canada for a period of three days. Three journals may be borrowed at a time. Periodicals are available from 1930 to date. Requests for issues of earlier date cannot be filled. Requests should be accompanied by stamps to cover postage (6 cents if one and 18 cents if three periodicals are requested). Periodicals published by the American Medical Association are not available for lending but can be supplied on purchase order. Reprints as a rule are the property of authors and can be obtained for permanent possession only from them.

Titles marked with an asterisk (\*) are abstracted below.

#### American Journal of Diseases of Children, Chicago 60:1245-1496 (Dec.) 1940

- Behavior Disorders of Intellectual Origin Occurring in Childhood. M. W. Thorner and G. H. J. Pearson, Philadelphia.—p. 145.
- Possible Relation Between Electrolyte Balance and Bronchial Asthma. A. V. Stoesser and M. M. Cook, Minneapolis.—p. 1252.
- \*Prophylaxis and Treatment of Whooping Cough with Pertussis Antigen: Report of Results. C. L. Joslin and T. A. Christensen, Baltimore.—p. 1269.
- Oral and Intravenous Dextrose Tolerance Tests in Cases of Acute (Catarrhal) Hepatitis. D. J. Pachman, Chicago.—p. 1277.
- Relation of Dental Caries in Rural Children to Sex, Age and Environment. B. R. East and Hilda Kaiser, New York.—p. 1289.
- \*Results of Schick Test in Children One to Ten Years After Injections of Toxoid. B. Benjamin, G. Fleming, Montreal, Canada, and Mary A. Ross, Toronto, Canada.—p. 1304.
- Olfactory Bulbs in Human Poliomyelitis. A. B. Sabin, Cincinnati.—p. 1313.
- Roentgenologic Study of Anomalies of Hands in 100 Cases of Mongolism. H. W. Hefke, Milwaukee.—p. 1319.
- Minimal Nitrogen Requirements of Children with Nephrotic Syndrome: Effect of Administration of Growth-Promoting Anterior Pituitary Extract. L. E. Farr, New York.—p. 1324.
- Respiration in Newborn Infants. A. R. Bauer, Detroit.—p. 1342.
- Meningitis Caused by Bacterium Coli Anaerogenes (Anaerogenic Coliform Organism): Report of Its Occurrence in a 3 Week Old Infant, with Temporary Cortical Insult and Recovery. S. Rauch and N. Krinsky, Brooklyn.—p. 1386.

**Pertussis Antigen for Prophylaxis and Treatment.**—Joslin and Christensen present results obtained with pertussis antigen (detoxified). The antigen had no effect with doses of 0.5, 0.8 and 1 cc. It was effective when the initial dose was increased to 1.5 cc. The authors had no standard on which to base the optimal dose, the most advantageous interval between doses or the total amount of antigen to be given. They divided their study into three parts: (1) the effect of the antigen on active pertussis, (2) its immunizing effect when administered as a routine to well children and (3) the influence on children exposed to pertussis but in whom sufficient time had not elapsed for the disease to develop. The antigen was given to 1,051 patients from 1 month to 10 years of age. The average duration of the attack was three and fifteen one-hundredths weeks. Twenty of the 1,051 patients treated showed no response to the antigen; they had severe pertussis. Reactions from the antigen were unusual. Occasionally a slight rise in temperature lasting twenty-four hours or a slight redness of the arm was observed. Three patients had an urticarial reaction. Thirteen patients who failed to return for further injections showed regression with progression of symptoms. In 6 of these patients there was a sluggish response to additional injections. There was a 94 per cent protection rate among children immunized with 6 cc. of antigen who were definitely exposed. In contrast, pertussis developed in 75 per cent of 200 children immunized with only 3 cc. of the antigen. The incidence of complications was reduced and the duration of the attack was shortened if the antigen was administered early. Results depended largely on the amount of antigen given per dose. Beyond a certain point additional antigen was of little value. Only 9 per cent of children receiving a second dose of 0.5 cc. responded, compared to 82 per cent of those patients receiving 1.5 cc. as a second dose. When a larger dose, 2 cc., was given the greatest response followed more equally the second and the third injections. The consistent increase of response corresponding to the increased amount of antigen given per dose is striking. The optimal interval between doses appears to be every second or third day; 82 per cent of the patients responded after four doses when the time interval

between doses was three days, as compared to 63 per cent when the interval was four days. The duration of immunity varied from five months to two and a half years. A number of infants immunized during this study with a mixed vaccine and antigen exhibited no appreciable protection. Of 118 children immunized after exposure 90 escaped pertussis, while 28 contracted the disease.

**The Schick Test After Injections of Toxoid.**—Benjamin and his associates Schick tested children who were available for study after receiving diphtheria toxoid from one to ten years ago. Children who had received less than two injections of toxoid or those given diphtheria antitoxin were not included. The group consisted of 1,522 children; 39 had had only two doses of toxoid and no previous Schick test, 78 had two doses and a previous Schick test, 517 had three doses and no previous Schick test, 853 had three doses and a previous Schick test, 8 had a second test after the third dose of toxoid and 27 had a second test after a fourth dose of toxoid. Of 1,251 children Schick tested from one to eleven years after the third dose of toxoid a positive reaction was elicited in 14.9 per cent from five to eleven years later. This was twice as great as that observed in from four to five years after the third dose of toxoid. Up to the end of the fifth year, the advantage seems to be with those who had a previous test. For the later years the advantage is not maintained and favors those not having a previous test. A previous Schick test would probably not increase the number of positive reactors, although it is possible that its stimulus may wear off after about five years. In none of the children did the Schick reactions revert from negative to positive in less than two years after the third dose of toxoid; in 8.4 per cent they did revert from negative to positive in from two to ten years. Diphtheria toxoid given to infants 6 months old achieved immunization which, as gauged by the Schick test, is as lasting as that in older children. The authors suggest that all children who receive three injections of diphtheria toxoid in infancy be given either a Schick test at 5 years of age and, if the reaction is positive, a further subcutaneous injection of 1 cc. of toxoid or, if the test is omitted, the recommended dose of toxoid at this age.

#### American Journal of Tropical Medicine, Baltimore 20:625-748 (Sept.) 1940

- \*Beriberi and Vitamin B<sub>1</sub> Deficiency. E. B. Vedder, Washington, D. C.—p. 625.
- Dry Season Observations on African Mosquito Anopheles Gambiae in Brazil in 1938. R. C. Shannon and G. C. de Andrade, Rio de Janeiro, Brazil.—p. 641.
- Effect of Change of Residence from Temperate to Tropical Climate on Basal Metabolism, Weight, Pulse Rate, Blood Pressure and Mouth Temperature of Twenty-One English and American Women. Eleanor D. Mason, Madras, India.—p. 669.
- Plasma Potassium Level During Malaria Infection in Monkeys and Man. R. L. Zwemer, E. A. H. Sims and L. T. Coggeshall, New York.—p. 687.
- Influence of Temperature on Plasmodium Vivax. W. K. Stratman-Thomas, Nashville, Tenn.—p. 703.
- Immunologic Studies in Malaria, with Special Reference to Diagnosis of Malaria. W. K. Stratman-Thomas and Anna Dean Dulaney, Nashville, Tenn.—p. 717.
- Natural Infection of Fetus with Leptospira Icterohaemorrhagiae in Wild Rat. T. G. Ward and T. B. Turner, Baltimore.—p. 727.
- Intestinal Content Cultivation Medium: I. Methods of Preparation and Use and Data Obtained in Cultivation of Balantidium Coli from the Pig. E. C. Nelson, Lewiston, Maine.—p. 731.

#### 20:749-898 (Nov.) 1940

- Observations on Naturally and Artificially Induced Quartan Malaria. M. F. Boyd, Tallahassee, Fla.—p. 749.
- Medicinal Prophylaxis of Amebiasis. C. F. Craig, San Antonio, Texas.—p. 799.
- Incidence of Intestinal Protozoa Among Freshman Medical and Dental Students, with Especial Reference to Amebiasis. H. Tsuchiya and J. T. Jean, St. Louis.—p. 803.
- Demonstration of Yellow Fever Antibodies in Animal Serums by Intracerebral Protection Test in Mice. J. C. Bugher, Bogota, Colombia, South America.—p. 809.
- Study of Serums of Lepers in Quantitative Complement Fixation Tests for Syphilis and Tuberculosis. Elizabeth Maltaner, Albany, N. Y.—p. 843.
- Residual Symptoms in Patients Following Recovery from Acute Infestation with Trichinosis. Z. Bercovitz, New York.—p. 849.
- Life Cycle of Plasmodium Relictum Variety Matutinum. R. D. Manwell, Syracuse, N. Y.—p. 859.
- Review of Literature on Exoerythrocytic Schizogony in Certain Malarial Parasites and Its Relation to Schizogonic Cycle in Plasmodium Elongatum. R. J. Porter and C. G. Huff, Chicago.—p. 869.

**Beriberi and Vitamin B<sub>1</sub> Deficiency.**—Vedder discusses the recent nutritional experiments on beriberi. A review of the work on vitamin B<sub>1</sub> suggests the possibility that degeneration of the nerves and the spinal cord may be produced by the deficiency of vitamins other than B<sub>1</sub>. Under certain circumstances deprivation of vitamin A is capable of producing degenerative changes in the nervous system in at least puppies, rats and fowls. It may have a similar effect on human beings subsisting on a diet deficient in fat and vitamin A. Synthesization from the B<sub>2</sub> complex of a few of its six or more factors, namely nicotinic acid, riboflavin and B<sub>6</sub> and the recognition of pantothenic acid as an unknown hydroxyacid and beta alanine, has shown that only the latter cures chick dermatitis. The paralysis and the accompanying changes in the peripheral nerves can be prevented by riboflavin. But neither riboflavin, nicotinic acid nor vitamin B<sub>1</sub> prevents degeneration of the spinal cord. Pantothenic acid was also most effective in eliminating pathologic changes in the spinal cord. The conclusion is that riboflavin is necessary to the growing chick for the normal functioning and maintenance of the nervous system and pantothenic acid for maintaining the structures of the spinal cord intact. From these experiments it is seen that in later years, as experimental diets have become more refined and the nature of the B<sub>2</sub> complex has been better understood, the results become increasingly definite and specific. Deprivation of certain factors of the B<sub>2</sub> complex can undoubtedly produce demyelination and degeneration of the axis cylinders of the peripheral nerves and of the spinal cord. There is no such definite experimentation on man. But applying these results to beriberi, it appears that persons living on an exclusive diet of polished rice, as many of the Oriental poor do, are as deficient in B<sub>2</sub> as they are in B<sub>1</sub>, and that the extensive nerve degeneration from which they suffer may well be chiefly due to deficiencies of vitamin A and vitamin B<sub>2</sub>. Those who in addition to the rice eat sufficient fish or meat do not suffer from B<sub>2</sub> deficiency. When deficiency of vitamin B<sub>1</sub>, A and certain factors of the B<sub>2</sub> complex exists, profound degeneration of the entire nervous system (a combination of dry and wet beriberi, the mixed disease) is produced which cannot be promptly cured by pure vitamin B<sub>1</sub>. A complete and adequate diet is the best treatment in these cases after preliminary treatment with thiamine.

## Archives of Dermatology and Syphilology, Chicago

42:993-1198 (Dec.) 1940

- \*Occupational Leukoderma. E. A. Oliver, Chicago; L. Schwartz and L. H. Warren, Washington, D. C.—p. 993.
- \*Ulcers of Legs in Sickle Cell Anemia. C. L. Cummer and C. G. LaRocco, Cleveland.—p. 1015.
- Massive Destruction of Face. C. C. Dennie, T. R. Hamilton and H. F. Quinn, Kansas City, Kan.—p. 1040.
- Acetylglucarsenobenzene in Treatment of Syphilis: Preliminary Report. W. H. Guy, B. A. Goldmann, G. P. Gannon and J. Slone, Pittsburgh.—p. 1046.
- Acute Disseminated Lupus Erythematosus: Its Treatment with Sulfanilamide and Allied Products. U. J. Wile and H. H. Holman, Ann Arbor, Mich.—p. 1059.
- Excretion of Bismuth in Urine of Patients Treated with Bismuth Ethylcamphorate. F. M. Thurmon and N. Benotti, Boston.—p. 1073.
- Action of Iodine on Diseases of Skin as Influenced by Season and Weather. F. R. Schmidt, Chicago.—p. 1083.
- \*Cutis Verticis Gyrata and Acromegaly. E. P. Zeisler, Chicago, and L. M. Wieder, Milwaukee.—p. 1092.
- Pityriasis-Rosea-like Dermatitis Following Gold Therapy: Report of Two Cases. U. J. Wile and C. J. Courville, Ann Arbor, Mich.—p. 1105.
- Hereditary Edema of Legs (Milroy's Disease) Associated with Other Congenital Anomalies. W. A. Rosenberg, Chicago.—p. 1113.

**Occupational Leukoderma.**—Oliver and his associates report the occurrence of leukoderma in a tannery. The investigation was requested by an insurance company. The men affected claimed that the depigmentation was the result of wearing a certain type of rubber glove. At the first visit to the tannery, where 88 persons were employed, 20 of the affected men were examined. Only 48 of the 88 employees wore the rubber gloves, and of those wearing gloves 25 (52 per cent) had leukoderma. The involved areas corresponded with those covered by the heavy rubber gauntlet type of glove worn. The areas of leukoderma were milky white. Even in the most pronounced cases the palms and the dorsal aspects of the terminal phalanges of the fingers were unaffected. The skin showed no signs of acute or chronic dermatitis. The pigment about the hair follicles seemed the last to disappear and the first to reappear. After a thorough investigation, including patch tests

of all the affected persons, an antioxidant added to the rubber for the purpose of improving its aging properties was found to be the cause. This antioxidant is known by the trade name agerite alba and is said to be the monobenzyl ether of hydroquinone. Patch tests made on unaffected volunteer subjects with the rubber and with the antioxidant in powder form, in a 75 per cent ointment and in a 20 per cent solution of alcohol, ether and collodion gave positive reactions in 2 cases. Tanning liquors played no part in the depigmentation. Investigation of all plants in which the particular gloves were worn by the workers showed the same type of leukoderma. The drug had no apparent effect on the general health of the persons; as examinations of the blood were within normal limits. The dopa reaction in biopsy specimens of the depigmented and repigmented skin was negative in the depigmented areas and positive in the repigmented ones. Repigmentation in many persons began soon after they ceased wearing the incriminating gloves. The authors believe that the monobenzyl ether of hydroquinone antioxidant has a physiologic action on the skin that other antioxidants do not have. At present they do not know how this drug acts on the cutaneous pigment. It apparently prevents the formation of melanin, either by action on the cells which form melanin or by action on one or more of the intermediate products in the formation of melanin from the amino acid tyrosine. The latter theory seems the more likely, as the cells do not appear damaged.

**Ulcers of Legs in Sickle Cell Anemia.**—Cummer and LaRocco report 5 cases of ulcers on the legs accompanying sickle cell anemia observed at St. Vincent Charity Hospital. They list the following available facts in an attempt to explain their causation: 1. Such ulcers occur in a definite proportion of persons suffering from sickle cell anemia and in a lower proportion of those with the sickle cell trait only. 2. They must be rare in pernicious anemia and chlorosis but they are encountered in congenital hemolytic jaundice. Their occurrence may be more frequent than is recognized now. 3. Murphy has advanced the opinion that sickle cell anemia may be the typical manifestation of familial hemolytic anemia in the Negro in whom, possibly because of some difference in the structure of the erythrocytes, sickle cells appear instead of spherical erythrocytes. 4. The ulcers in sickle cell anemia seem to have been induced, or at least preceded, by infection or trauma. Their size and duration are out of all proportion to the infection or trauma. 5. They show no specific distinguishing histologic features from other chronic ulcers. The authors advance the following theories: 1. The ulcers have been produced by injury or infection and have become chronic because of associated malnutrition or the lowered vitality of anemic tissue. 2. Against this is the apparent lack of evidence that similar lesions occur in other severe anemias, notably chlorosis, which affects adolescent girls of the same age as those with sickle cell anemia in whom ulcers of the legs develop most frequently. That they are coincidental is not plausible, as they occur more often in sickle cell anemia than in the sickle cell trait. 3. Capillary blocking as a cause would not explain similar ulcers in chronic hemolytic jaundice, in which thromboses are not a part of the process and the erythrocytes are not elongated but spherocytic. The ulcers are usually punched out, may be single or multiple and unilateral or bilateral and usually occur at the ankle. Their course is extremely chronic. Simple local applications seem the most effective treatment. The microscopic picture is that of chronic granulomatous ulcers. Anemia should be considered as a possible explanation for old chronic ulcers on the legs, especially in younger persons.

**Cutis Verticis Gyrata and Acromegaly.**—Zeisler and Wieder believe from study of the literature and consideration of their own 2 cases that cutis verticis gyrata may be added to other clinical signs pointing to pituitary disease. It may be the only external sign and therefore be overlooked. Such was the case in 1 of their patients. Although the condition was observed in only a few instances of acromegaly described in the literature, it is probable that more may have had this early sign of oncoming pituitary disease than were recognized. Because of this, the authors wish to reemphasize the need for careful study, with the inclusion of routine roentgen examination of the skull and



extremities of this group of cases. The finding of a sella normal in size on roentgen study does not necessarily negate the diagnosis of associated cutis verticis gyrata with acromegaly. This was illustrated by Sisson's case, which, although one of frank acromegaly, showed a sella of apparently normal size. Dermatologists may be the first to see these patients, and their prompt recognition of its significance may bring about the detection of a serious underlying disease. The authors believe, to the best of their knowledge, that they are citing the third and fourth instances of cutis verticis gyrata associated with pituitary disease to be reported in the American literature. The first was reported by Sisson and the second by Cushing and Davidoff, who termed the disorder "bulldog scalp." Occasionally brain surgeons have accidentally encountered this anomaly in the course of operations on the pituitary.

### Journal of Immunology, Baltimore

39:369-440 (Nov.) 1940

- Effect of Dilution on Reaction Between Pneumococcus and Its Specific Antibody. M. C. Morris, St. Louis.—p. 369.  
Role of Diffusion in Pneumococcus-Antipneumococcus Reaction. A. D. Hershey, St. Louis.—p. 383.  
Serology of Pneumococcus Group. F. Kauffmann, E. Mörch and K. Schmitt, Copenhagen, Denmark.—p. 397.  
\*Studies on Immunization of Adults with Diphtheria Toxoid. C. P. Bunch, R. C. Morrow Jr., J. R. Timmons and D. T. Smith, Durham, N. C.—p. 427.

#### Immunization of Adults with Diphtheria Toxoid.—

After studying the various procedures recommended for the immunization of adults with diphtheria toxoid and from their observations on 90 Schick positive subjects, Bunch and his associates found the intracutaneous injection of minute doses of toxoid to be an easy regimen. Twenty-six of 27 such subjects became Schick negative, leaving only 1 to undergo a series of graded subcutaneous doses. The plan they adopted for the whole group is as follows: A Schick test is made on the persons to be immunized and a Moloney test on the Schick positive individuals. The M— and M+ reactors are given as a routine 2 cc. of undiluted toxoid in 1 cc. subcutaneous doses at intervals of one month. The M++ and M+++ reactors are given three 0.1 cc. intracutaneous injections of toxoid used for the Moloney test (a 1:100 dilution of toxoid) at weekly intervals. Schick tests are performed from three to six months after the last injection. If any M++ or M+++ subjects remain Schick positive, they are inoculated with a series of graded subcutaneous injections.

### Laryngoscope, St. Louis

50:1025-1106 (Nov.) 1940

- Review of Available Literature on Pharynx and Pharyngeal Surgery for 1939. F. E. LeJeune and P. J. Bayon, New Orleans.—p. 1025.  
Information Please: Regarding Hearing Aids and Audiometers. F. T. Hill, Waterville, Maine.—p. 1054.  
Polypoid Tumors of Esophagus: Report of Two Cases. J. J. Mahoney, New York.—p. 1086.  
Some Problems in Nasal Plastic Surgery. C. R. Straatman, New York.—p. 1092.  
Are Unwise Efforts Being Made to Connect the Avenue of Infection in Poliomyelitis to Trauma Following Adenoid and Tonsil Operations? Does an Unknown Port of Entry, Uncertain Incubation Period and Debatable Strain of So-Called Filtrable Virus Warrant Any Such Assumption? H. G. Langworthy, Dubuque, Iowa.—p. 1100.

### New England Journal of Medicine, Boston

222:877-916 (Nov. 28) 1940

- \*Sulfathiazole Therapy of Staphylococcus Aureus Bacteremia. C. H. Rammelkamp and C. S. Keefer, Boston.—p. 877.  
Tularemia: Report of Case Contracted on Cape Cod. R. E. Moss and L. R. Evans, Boston.—p. 885.  
Pneumococcal Cross Infections in the Home and Hospital. H. A. Holle and J. G. M. Bullowa, New York.—p. 887.  
Hodgkin's Disease: Report of Case with Unusual Longevity and Invasion of Heart and Pericardium. M. Ritvo, Boston.—p. 891.  
Multiple Pulmonary Thrombi Associated with Cyanosis and Right-Sided Cardiac Hypertrophy: Report of Case. V. G. Balboni, Boston.—p. 896.  
Treatment of Juvenile Diabetes Mellitus. A. M. Butler, Boston.—p. 900.

**Sulfathiazole for Staphylococcus Aureus Bacteremia.—**Rammelkamp and Keefer cite 7 cases of Staphylococcus aureus bacteremia in which sulfathiazole was administered. In addition they studied the bactericidal properties of the blood obtained

from 3 patients and from 5 normal persons following the oral administration of sulfathiazole. The number of cases treated is too small to judge the efficacy of the therapy. Age and the accessibility of metastatic abscesses to surgical drainage are important factors influencing the course of the disease. Prognosis is considered grave after 40; 4 of the patients, 1 of whom recovered, were 40 or more years of age. In the 3 patients who recovered the abscess was drained. In 1 of these there was, in addition to the abscess in the right thigh, an empyema that became sterile during sulfathiazole therapy. Surgical drainage of localized staphylococcal abscesses seems essential to recovery in most cases. The blood studies show that sulfathiazole when given by mouth to normal persons and to patients with bacteremia increases the bactericidal and bacteriostatic action of the blood against pathogenic staphylococci. Therefore the authors believe that sulfathiazole either sterilized the blood stream or lowered the number of organisms in the circulating blood. This may be valuable in preventing metastatic abscesses during invasion of the blood stream. The development of these metastatic abscesses (in 82 per cent of cases) which cannot be drained determines the fatal outcome in the majority of cases. The level of sulfathiazole in the blood stream should be between 3 and 5 mg. per hundred cubic centimeters. If the patient is anemic, blood transfusions should be given until the blood count is normal. Immediate drainage of all localized abscesses is of the utmost importance. A sustained fever or continuously positive blood cultures are usually signs of further abscess formation, and they should be searched for thoroughly. Toxic manifestations should be watched for and daily blood counts and urine analyses should be made. In the cases reported no serious toxic manifestations were observed.

### New York State Journal of Medicine, New York

40:1693-1760 (Dec. 1) 1940

- Development of Voluntary Health Insurance in the United States. D. K. Freedman and Elinor B. Harvey, New York.—p. 1699.  
Hazards of Pregnancy and Labor in the "Grande Multipara." N. J. Eastman, Baltimore.—p. 1708.  
Certain Eye Factors in Prevention of Motor Vehicle Accidents. C. Berens, New York.—p. 1713.  
The Elmira Tumor Clinic: Survey of Work After Six Years of Its Existence. M. Dreyfuss, Elmira.—p. 1725.  
Emphysema: Dominant Finding in Acute Respiratory Infection: Preliminary Report of Possibly New Clinical Picture. Margaret R. Reynolds, Jackson Heights.—p. 1729.

### Oklahoma State Medical Assn. Jour., Oklahoma City

33:1-58 (Nov.) 1940

- Hypertension. C. A. Traverse, Alva.—p. 1.  
Pellagra. V. H. Musick, Oklahoma City.—p. 4.  
Value of Metrazol Convulsive Shock in Psychiatric Therapy. G. W. Robinson Jr., Kansas City, Mo.—p. 8.  
Sinus Disease in Children. C. H. Hall, Oklahoma City.—p. 12.  
Modernizing Medical Public Relations. H. T. Sethman, Denver.—p. 16.

### Public Health Reports, Washington, D. C.

55:2195-2250 (Nov. 29) 1940

- Tumor Clinic of the Baltimore Marine Hospital. E. R. Bryan.—p. 2195.  
National Health Survey: Receipt of Medical Services in Different Urban Population Groups. R. H. Britten.—p. 2199.  
Colorado Tick Fever. N. H. Topping, J. S. Cullyford and G. E. Davis.—p. 2224.

### Radiology, Syracuse, N. Y.

35:521-650 (Nov.) 1940. Partial Index

- Roentgen Ray Examination with Miller-Abbott Tube. R. Golden, Octa C. Leigh and P. C. Swenson, New York.—p. 521.  
Roentgenologic Findings in Acute Obstruction of Colon, with Particular Reference to Acute Volvulus of Sigmoid. L. G. Rigler and O. Lipschultz, Minneapolis.—p. 534.  
Behavior of Small Intestine During Urinary Tract Irritation. K. D. A. Allen and J. H. Jamison, Denver.—p. 544.  
Role of Intestinal Intubation in Diagnosis and Localization of Intestinal Obstruction. J. E. Lofstrom and R. J. Noer, Detroit.—p. 546.  
Treatment of Cancer of Lip and Mouth. G. E. Pfahler, Philadelphia.—p. 598.  
Use of Zinc Peroxide in Infected Tumors and Radiation Necrosis: Report of Cases, with Technic. D. A. Sunderland and J. S. Binkley, New York.—p. 606.  
Roentgen Diagnosis of Cholecystocolic Fistula. C. A. Stevenson and M. W. Sherwood, Temple, Texas.—p. 616.  
Familial Brachyphalangy. M. D. Sachs, Portland, Ore.—p. 622.

**Rhode Island Medical Journal, Providence**

23:205-222 (Dec.) 1940

- X-Ray Study as Aid to Diagnosis of Placenta Praevia. P. Appleton, Providence.—p. 205.  
 Report of Bagging Cases at Providence Lying-In Hospital: Jan. 1, 1926 to Dec. 31, 1938, Period of Thirteen Years. C. S. Houston, Providence.—p. 207.  
 Providence Lying-In Hospital Toxemia Clinic: Preliminary Report. W. S. Jones, Providence.—p. 209.

**Surgery, Gynecology and Obstetrics, Chicago**

71:697-830 (Dec.) 1940

- \*Venography, Clinical Study. J. Dougherty and J. Homans, Boston.—p. 697.  
 Differentiation of Benign from Malignant Polypoid Bronchial Tumors. H. Brunn and A. Goldman, San Francisco.—p. 703.  
 \*Factors in Recurrence of Varicosities Following Treatment. L. K. Stalker and W. W. Heyerdale, Rochester, Minn.—p. 723.  
 Studies in Malignant Testis Tumors: III. Incidence and Nature of Tumors in Ectopic Testes. J. B. Gilbert, Schenectady, N. Y., and J. B. Hamilton, New Haven, Conn.—p. 731.  
 Estrogen Therapy of the Climacteric: Analysis of Seventy-Seven Personal Cases. E. C. Smith, New Orleans.—p. 744.  
 \*Benign and Malignant Cystic Tumors of Appendix. R. Woodruff and J. R. McDonald, Rochester, Minn.—p. 750.  
 Adenosis of Vagina and Its Relation to Primary Adenocarcinoma of Vagina. A. Plaut and M. L. Dreyfuss, New York.—p. 756.  
 Use of Asparagin Bacteriophage in Treatment of Acute Hematogenic Osteomyelitis. P. S. MacNeal, Ann Arbor, Mich.—p. 766.  
 Correlation Between Clinical and Experimental Findings in Cases Showing Invasion of Blood Stream by Staphylococci. B. Kleiger and J. E. Blair, New York.—p. 770.  
 Preparation and Preservation of Sterile Citrated Blood Plasma by Ampule Tube Method. R. T. Crowley, Detroit.—p. 777.  
 Webbed Fingers. D. W. MacCollum, Boston.—p. 782.  
 Pedicle Tube Graft in Surgical Treatment of Hypospadias in the Male, with New Method of Closing Small Urethral Fistulas. D. M. Davis, Philadelphia.—p. 790.  
 Method for Prevention of Spread of Osteomyelitis of Bones of Skull. W. P. Van Wagenen, Rochester, N. Y.—p. 797.  
 Recurrent Inguinal Hernia: Importance of Artificial Fibroplastic Proliferative Phase in Hernia Repair. C. L. Wilmoth, Pittsburgh.—p. 802.  
 Device for Making Accurate Roentgenograms of Neck of Femur During Reduction. H. McKenna, Chicago.—p. 808.  
 Surgical Treatment of Ectopic Testes. O. S. Lowsley, New York, and H. C. Curtis, Hamilton, Bermuda.—p. 811.  
 Breech Delivery. W. D. Hawker and S. D. Soule, St. Louis.—p. 819.

**Venography.**—Dougherty and Homans made venograms in 15 cases, 6 of which were normal and 9 abnormal. There was no reaction to the diodrast (an organic iodide). In the normal cases the solution passed freely into both the deep and the superficial circulation. In 1 or 2 of the earlier cases the superficial circulation filled more readily than the deep, probably because the injection was made directly into one of the small tributaries of the greater, rather than the lesser, saphenous system. In practically every abnormal case there was rather pronounced resistance to the rate of injection. A greater force was required to cause the solution to enter the deep circulation and a longer time was necessary to complete the injection. This may have been due to venospasm or mechanical blocking of the circulation. In a few instances the roentgen results suggested spasm, but in others it seemed that the irregular outline of a thrombus could be seen or that the opaque substance failed to enter the vessel because it was blocked. In several instances light compression by rubber tubing, usually above the knee, had little effect on causing the diodrast-laden blood to enter the deep circulation. The direction of flow evidently depended on the existence of some intrinsic factor such as thrombosis or spasm of the wall of the vessel and not on limited expansion by periphlebitis or generalized edema of the tissues of the extremity. The authors limited their investigation to the lower extremities and the adjacent portions of the body and were principally concerned with thrombosis. They cite 2 of their cases; the first was one of acute femoro-iliac thrombophlebitis accompanied by arterial spasm and the second a case of traumatic femoro-iliac thrombosis, subsequently canalized and complicated by recurrent small embolisms.

**Recurrence of Varicosities Following Treatment.**—Stalker and Heyerdale state that more than 50 per cent of the patients with varicosities of the lower extremities treated at the Mayo Clinic have associated incompetent great saphenous veins. A high incidence of recurrence has been observed when simple injection treatment was carried out. This has been eliminated

by division and ligation of the great saphenous vein together with the injection of sclerosing solutions into the portion of vein distal to the ligation at the saphenofemoral junction, together with separate division and ligation of its uppermost tributaries. Recurrence has been reported even after this treatment. In the authors' experience the incidence of recurrence in this group has been exceedingly small. For the most part these recurrences can be prevented if the many variations in the anatomy of the great saphenous vein and its tributaries at the fossa ovalis are recognized and adequately treated at operation. After careful clinical study and examination at the first and second operations they believe that the recurrences have been due to technical mismanagement of the primary operation. Probably the tendency toward varicosities cannot be eliminated entirely. Unless the variations in the anatomic relationships of the great saphenous vein, its tributaries and surrounding structures around the fossa ovalis are recognized, some condition which may result either in a complete or a partial operative failure with resulting persistence or recurrence of an incompetent great saphenous system may be overlooked. The continuity of the veins of the lower extremity with those of the abdomen explains canalization of a thrombosed vein or dilatation of collateral vessels that act as shunts around the site of ligation of the saphenofemoral junction. Through these shunts hydrostatic pressure, augmented by spasmodically variable intra-abdominal pressure, is brought to bear on the veins distal to the ligation. Therefore it is necessary to divide and ligate separately, at the proper site, not only the great saphenous vein but also its tributaries. The relationship of these tributaries to the parent vein is not always constant, and a sufficiently wide exposure is necessary for their proper identification. Extreme care must be exercised, as a dilated superficial femoral vein may be mistaken for the great saphenous vein. The failure to excise a segment of vein may lead to recurrence owing to canalization. The injection of a sclerosing solution into the portions of divided veins distal to the ligation is of definite advantage.

**Benign and Malignant Cystic Tumors of Appendix.**—Woodruff and McDonald point out that from January 1914 to July 1938 approximately 43,000 appendectomies were performed at the Mayo Clinic. Examination of the appendixes disclosed 136 to have a so-called mucocoele and 10 a grade 1 adenocarcinoma in a cyst. This incidence (0.3 per cent) agrees favorably with reports in the literature. The youngest patient among the 136 with simple mucocoeles was 4 and the oldest 70 years of age. This group was studied individually. The authors concluded that mucocoeles of the appendix are the result of stricture of the lumen, which usually is caused by inflammation. The benign nature of the growths was established. For the cystocarcinomas the hypothesis is presented that they are the result of malignant change in the wall of the benign mucocoele. Simple mucocoeles seem to have little clinical importance. At times a benign cyst of the appendix may be the cause of vague symptoms, but on the whole it has little significance. Cystocarcinomas of the appendix rarely reach clinical stages, but potentially they may rupture and be the cause of pseudomyxoma peritonei with a lethal outcome. The authors believe that the opinion of many other workers that pseudomyxoma peritonei of appendical origin is less malignant than that originating in the ovary is erroneous and is due to the fact that many of the reported cases were not really malignant but due to the escaping of the innocuous contents of benign cysts into the abdominal cavity. On the other hand, the fatal cases probably all originated in a carcinomatous cystadenoma of the appendix.

**Wisconsin Medical Journal, Madison**

39:897-996 (Nov.) 1940

- The Doctor and Democracy. E. J. Carey, Milwaukee.—p. 915.  
 What Confronts America and the Western Hemisphere Today. R. M. Immell, Madison.—p. 924.  
 Industrial Health as It Relates to National Preparedness. S. J. Seeger, Milwaukee.—p. 929.  
 Perinephric Abscess: Review of Twenty-One Cases, with Special Reference to Anaerobic Infection. B. B. Madison, Springfield, Ill.—p. 932.  
 Cardiovascular System as Related to Surgical Risk. W. T. Carpenter, Milwaukee.—p. 935.  
 New Use for an Old Idea. R. H. Gray, La Crosse.—p. 938.  
 Maternal Care and Maternal Mortality, with Special Reference to Progress in Wisconsin. E. F. Daily, Washington, D. C.—p. 940.  
 Wisconsin Marches On. Amy Louise Hunter, Madison.—p. 944.

## FOREIGN

An asterisk (\*) before a title indicates that the article is abstracted below. Single case reports and trials of new drugs are usually omitted.

## British Journal of Dermatology and Syphilis, London

52:321-352 (Nov.) 1940

- Treatment of Pruritus Vulvae, Leukoplakia and Kraurosis. Agnes Savill.—p. 321.  
Two Severe Dermatoses Treated with Sulfonamide Preparation. H. MacCormac.—p. 339.

## Lancet, London

2:537-576 (Nov. 2) 1940

- The Moynihan Tradition. G. Gordon-Taylor.—p. 537.  
Reality of Partial Deficiencies. L. J. Harris.—p. 539.  
Estimation of Blood Volume in Plasma Transfusion. S. R. M. Bushby, A. Kekwick and L. E. H. Whitby.—p. 540.  
Galactose Tolerance Test in Experimental Liver Necrosis. E. J. King, C. V. Harrison and G. E. Delory.—p. 541.  
\*Intravenous Galactose Tolerance Test. E. J. King and R. S. Aitken.—p. 543.  
\*Effect of Calcium on Diuresis in Cardiac Decompensation. N. Morris and A. S. Rogen.—p. 545.  
Splints for Fingers and Thumb. W. I. de C. Wheeler.—p. 546.  
Polyradiculoneuritis (Guillain-Barré's Syndrome) in East Anglia. H. S. Barber.—p. 548.  
Morbidity and Death Rates in the Great Towns. P. Stocks.—p. 550.

**Intravenous Galactose Tolerance Test.**—According to King and Aitken the oral galactose tolerance test introduced by Bauer in 1906 is only a rough test of liver function. The rate of absorption of galactose is greater than that of any other sugar in the rat. This led to the belief that galactose is an ideal substance for use in tolerance tests. But its rate of absorption in man is variable and, after 40 Gm. has been taken by mouth, the blood galactose may be anything from a few milligrams to 60 mg. per hundred cubic centimeters. This great variation in the peak of the blood galactose curve suggested that a more satisfactory procedure would be to give the sugar intravenously to insure flooding of the system with galactose at the beginning of the test. The rate at which galactose disappeared from the blood should then furnish some measure of the glycogenic function of the liver, which is the principal tissue concerned with its conversion into glycogen. Intravenous galactose tolerance tests have been employed for some years. In these tests a relatively small dose of galactose (from 8 to 10 Gm. in a 40 per cent solution) was administered and the total blood sugar estimated at short intervals for from one half to one hour. King, Harrison and Delory tested the hepatic function of animals with artificially produced liver damage after the administration of large amounts of sugar. This work led to a study of liver function tests and to the development of an intravenous galactose test for application in man. The authors describe the technic and results of a galactose tolerance test of hepatic dysfunction in which 50 cc. of a 50 per cent solution of galactose is injected intravenously and the blood galactose is determined at half hour intervals thereafter. This modification of the galactose tolerance test is free from theoretical objections, and the results given show that in nearly all cases it distinguishes clearly between jaundice due to liver cell damage and jaundice due to gross obstruction of the biliary tract without liver cell damage. That is its practical value; it is not suggested that it will detect minor grades of liver damage in patients who are not jaundiced.

**Calcium for Diuresis in Cardiac Decompensation.**—Morris and Rogen point out that in many patients with cardiac failure one of the objects of treatment is to get rid of edema fluid and that calcium salts have been used to aid the diuretic action. Most of the work previously undertaken on the diuretic action of calcium has been done with the chloride, which probably owes its efficiency to its acid-producing effect. In the present investigation it was desired to determine the effect of calcium uninfluenced by tendency to acidosis. Accordingly calcium gluconate was used; in later cases solution of parathyroid was employed to raise the concentration of calcium in the serum. Calcium gluconate was administered intravenously to 10 patients with cardiac edema. It had little immediate effect on the urinary output. In 6 of 7 patients who had previously been receiving digitalis the diuretic effect of this drug was increased when given

after a course of injections of calcium gluconate. In 9 of 10 patients with cardiac edema, injections of solution of parathyroid enhanced the diuretic action of salyrgan and digitalis.

2:577-610 (Nov. 9) 1940

- Virus Diseases Acquired from Animals. S. P. Bedson.—p. 577.  
Exophthalmic Ophthalmoplegia. H. G. McGregor.—p. 579.  
\*Combined Immunization with Tetanus Toxoid and T. A. B. I. H. Maclean and L. B. Holt.—p. 581.  
Traumatic Rupture of Infrapatellar Tendon: Results of Repair by Fascial Suture. W. A. Cochrane.—p. 583.  
Hemorrhagic Thrombocythemia. J. Reid.—p. 584.  
\*Effect of Smoke on Bacteria in Air. C. C. Twort and A. H. Baker.—p. 587.  
Fatal Pellagra in an English Schoolgirl. R. E. H. Simpson.—p. 589.

**Combined Tetanus Toxoid and T. A. B. Immunization.**—Maclean and Holt point out that twenty-four years ago simple typhoid vaccine was combined with paratyphoid vaccine in the formula which is generally known as T. A. B. Immunization with this vaccine is accomplished by two doses administered at an interval of from seven to ten days. Ramon and Zoeller were the first to immunize large numbers of human subjects with tetanus toxoid, and various systems of dosage of tetanus toxoid were tried. Ramon and Zoeller then demonstrated that if tetanus toxoid is administered with T. A. B. vaccine the antitoxic response to the toxoid is greater than if it is given alone. The method used by Ramon is three doses of the vaccine-toxoid mixture with intervals of two or three weeks between doses. Maclean and Holt wished to immunize men simultaneously against tetanus and the enteric fevers with the minimum number of inoculations and found that the simplest effective method was to give two doses of the combined antigens (T. A. B. T.) at an interval of four weeks. The response to the antigens of the T. A. B. vaccine was as good as if these were administered at the usual short interval of one week. The amount of tetanus antitoxin in the serum of the immunized man was more than five times as great as it was in those who had two doses of tetanus toxoid alone at intervals of four or six weeks. Every subject tested who had been immunized with two doses of T. A. B. T. at a four weeks interval had an antitoxic titer of more than 1 unit of antitoxin per cubic centimeter in his serum, which is much higher than that which is accepted as an immunizing level against tetanus. In 50 per cent the antitoxic titer rose to 5 units or more per cubic centimeter, which is many times higher than would be reached by the usual prophylactic dose of tetanus antitoxin. The reaction to the combined antigens (T. A. B. T.) was no greater than to the T. A. B. vaccine alone.

**Effect of Smoke on Bacteria in the Air.**—In the course of investigations on germicidal aerosols, Twort and Baker examined the possibility of interference with the activity of the germicide mists by different kinds of smoke, more especially tobacco smoke. They found that exhaled tobacco smoke interfered with the effect of a phenolic germicidal aerosol in a concentration of 1 Gm. in 680 cubic meters of air on a suspension of *Escherichia coli*. Smokes produced by six smoldering organic substances were lethal to four bacterial suspensions tested, the flora of a normal saliva being much more sensitive than broth emulsions of three laboratory cultures. Cardboard and incense were the most satisfactory materials used, there being evidence of some lethal effect of the incense smoke in a concentration of 1 Gm. in 3,000 cubic meters of air after half an hour's contact with the atomized saliva. In calculating concentrations of smoke no account has been taken of unburned carbon, ash or material passing into the air as vapor (presumed inactive as germicidal aerosols). Estimations, by aspiration, of the actual quantity of smoke present in the air under test resulted in the recovery of only about 25 mg. for every 100 mg. of crude incense burned. Incense smoke, under the experimental conditions, persists in the particulate form, liquid or solid, for at least half an hour. Magnesium oxide and ammonium chloride smokes in a concentration of 1 Gm. in 10 cubic meters of air had no apparent lethal effect on an atomized broth emulsion of a laboratory culture. Infection of the respiratory apparatus of mice with a bacterial suspension of *Salmonella enteritidis* ("Liverpool virus" strain) was mostly prevented by decontamination of the air with cardboard and incense smokes in a concentration lower than 1 Gm. in 30 cubic meters of air.

## Presse Médicale, Paris

48:681-688 (Aug. 28-31) 1940

\*Thymectomy for General Asthenia with Marked Retardation of Growth and Puerility: Case. R. Leriche and A. Jung.—p. 681.  
Experimental Studies of Pulmonary Embolus. G. Pascalis.—p. 682.

**Thymectomy for Asthenia and Growth Retardation.**—Leriche and Jung report the case of a girl aged 17 years but presenting the appearance of a child from three to four years younger, with a history of chronic fatigability and progressive physical and mental debility, in whom ablation of the thymus effected a veritable transformation. The patient had undergone an appendectomy four years earlier, making an uneventful recovery, and two years later had had an attack of measles, which was of short duration but required three months for recovery. An assumed endocrine insufficiency had been vainly combated with appropriate medication. At the time of hospitalization, the patient weighed 88 pounds (40 Kg.) and complained of being always cold and tired. Any serious effort prostrated her and necessitated excessive sleep. Clinical observations and numerous roentgen tests disclosed no pathologic condition of the organs and revealed no thymus. The only diagnostic indications were the poor physical appearance, extreme fatigability and a dry skin. Guided by a similar previous experience, the authors had recourse to thymectomy. A quite well developed, very active thymus was found, forming a compact pinkish white mass 11 cm. in length and weighing 25 Gm., attached to the posterior sternum. Microscopic examination showed the presence of numerous Hassall's corpuscles without pathologic characteristics. The patient was discharged at the end of a week and already at that time showed a remarkable change. Seen two months later, she could walk, run and work without fatigue and had undergone within a few weeks a brisk body growth. However, there was no increase in body weight and the skin was still dry. Later reports by a qualified observer indicated progressive improvement along normal lines. The authors admit that thymectomy in a syndrome inexplicable on physical and endocrine grounds and presenting only slender clues to work on, in which other therapeutic measures have failed, must be regarded as a decision of desperation.

## Semana Médica, Buenos Aires

47:961-1028 (Oct. 31) 1940. Partial Index

\*Treatment of Cervicitis by Mendez's Treatment of "Closed Cavity" for Immunity. R. Pastorini.—p. 994.  
Vitamin C in Treatment of Hemorrhages. A. Carelli.—p. 1016.

**Mendez's Treatment of Cervicitis.**—Pastorini reports results obtained with vaccines prepared from bacterial haptenes and administered according to the "closed cavity" method of Mendez. References to this method of producing immunity were made in the *Semana Médica* May 14, 1936 and Jan. 28, 1937 and abstracted in *THE JOURNAL* July 18, 1936 page 245 and March 27, 1937 page 1144, respectively. The merit of the treatment consists in maintaining the exudate of a given cavity in direct contact with local tissues. Organic exudates contain antibodies which, in association with the injected haptenes, stimulate a local reaction through which the exudates are rendered sterile. Haptenes of either gonococcal or pyogenic bacteria of the same type identified in the vaginal secretion are used in the treatment of cervicitis. The vaccine is injected into the wall of the neck of the uterus, one hour after intramuscular injection of 1 cc. of milk. Immediately after the injection of the vaccine, a suppository containing vaccine of the same type is left in the vagina and the latter is packed with sterile gauze, thus forming a local "closed cavity." The treatment is repeated at intervals of two or three days in cases of acute cervicitis and of four days in chronic cervicitis. Clinical and bacteriologic cure takes place after three or four injections in the majority of cases and after six or seven injections in the exceptional case. Follow-up of the late results of the treatment of 133 patients revealed that in a group of 121 who had had a complete treatment 115 obtained a permanent result. The treatment is harmless, economical, produces rapid satisfactory results and can be administered to pregnant and nonpregnant women.

## Münchener medizinische Wochenschrift, Munich

87:741-768 (July 12) 1940. Partial Index

Attitude Toward Treatment of Gas Edema. W. Wachsmuth.—p. 741.  
Problem of Interruption of Pregnancy During Herpes Gestationis. J. Mayr.—p. 742.  
\*Causes of General Decalcification of Skeleton. H. Hellner.—p. 743.  
Corpus Luteum Hemorrhage as Vital Indication for Operation. F. Pelmer.—p. 747.  
Dosage of and Tolerance for Azosulfamide. E.-H. Garkisch.—p. 748.  
Knee Phenomena and New Maneuver for Their Elicitation in Multiple Neuritis (Pseudotabes Polyneuritica). A. Knapp.—p. 749.

**General Decalcification of Skeleton.**—Hellner maintains that every generalized decalcification of the skeleton is due to a disturbance in the calcium-phosphorus metabolism. Osteogenesis imperfecta is a hereditary defect. The entire skeleton is deficient in calcium and is abnormally fragile. Since osteogenesis imperfecta develops in spite of an adequate calcium content of the food, a defective utilization of the calcium is assumed. It has been found that the calcium and phosphorus values of the serum are increased in osteogenesis imperfecta, but the activity of the osteoblasts is apparently defective. The fragility of the bones is accompanied by blue sclerae, otosclerosis and occasionally disturbances in the development of the hair, the teeth and the nails, which indicates a hereditary impairment of the entire mesoblast. The hereditary defect may be apparent immediately after birth or it may become apparent later. Osteitis fibrosa generalisata is a form of skeletal decalcification which is due to endocrine disturbances, that is, to abnormal function of the parathyroids. However, the hypertrophy of the parathyroids is a secondary disturbance in skeletal decalcification, representing an effort at regulation of a disordered calcium content. Every disturbance in the calcium-phosphorus metabolism which is followed by decalcification of the skeleton influences the activity of the parathyroids and becomes manifest in their hyperplasia. This can be observed in osteomalacia, in rickets, in osteoporosis that develops in the presence of biliary fistulas, in Cushing's disease or renal and intestinal acidoses, in skeletal carcinoma, in multiple myelomas and in osteitis deformans. That hereditary constitutional factors play a part is proved by the occurrence of unilateral cases of osteitis fibrosa generalisata, for unilaterality can be only of genetic origin. Vitamin deficiencies may cause skeletal decalcifications, and the production of hormones is also largely dependent on adequate supplies of vitamins. Deficiency in vitamin D leads to skeletal decalcifications; rickets and osteomalacia are clinical manifestations of this. Decalcification of the skeleton in vitamin C deficiency is due to deficient osteoblastic activity. In the general skeletal decalcifications resulting from metabolic disturbances, acidosis plays an important part because the removal of excessive acids requires free calcium ions which are withdrawn from the skeleton. Disturbances in the intestinal absorption of calcium may likewise be a cause in general skeletal decalcification. Deficient absorption of calcium has been observed in pyloric stenosis and after total gastric resection. Osteoporosis, particularly of the spinal column, has been observed after prolonged use of laxatives. The etiology of skeletal decalcification varies widely. It is possible to differentiate between a hereditary disturbance in the skeletal utilization of calcium, a pathologic elimination of calcium from the skeleton, a deficient oral intake, a pathologic withdrawal from the skeleton as the result of metabolic disturbances or of an insufficient absorption in the intestine. Several of these disturbances may be combined. The treatment must consider the different etiologic factors.

## CORRECTION

**"Pervitin."**—In the abstract of an article on Prophylaxis of Prolonged Coma in Insulin Shock by Accornero and Giordani in *THE JOURNAL*, Nov. 23, 1940, page 1835, reference was made to "1-phenol-2-methylaminopropanol." The correct name should have been "1-phenyl-methyl-aminopropane"—a drug apparently marketed in Germany under the name "Pervitin," manufactured by the Temmler-Werke, Vereinigte Chem. Fabriken, Berlin-Johannisthal, Germany. The Council on Pharmacy and Chemistry has found no evidence to show that the drug is available on the American market. Furthermore, under the new Food and Drug Act it would be necessary for the drug to be licensed for sale and interstate commerce. The preparation is related chemically to ephedrine, benzedrine and propadrine.

# THE STUDENT SECTION

of the

## Journal of the American Medical Association

*Devoted to the Educational Interests and Welfare of Medical Students, Interns and Residents in Hospitals*

SATURDAY, JANUARY 25, 1941

### A Study of the Medical Education of Women

KATE CAMPBELL HURD-MEAD, M.D.

HADDAM, CONN.

From century to century medical women as well as men have had interesting and important careers. There has been no age in which the two sexes have not worked side by side in order to improve the health and the happiness of the people around them as well as to augment their own fortunes.

#### FROM THE FIRST TO THE FIFTEENTH CENTURY, A. D.

In the first century A. D., while Greek manuscripts were being translated into Latin, Soranus and Celsus and other learned men of Rome were making the hippocratic teachings in gynecology and pediatrics their own. A hundred or more years later Galen also copied and vastly increased what Soranus and Celsus had copied, but he used the medical material not only of other men but also of women doctors, among whom were an Aspasia, a Metrodora, a young Cleopatra and a little woman from Africa who was a classmate of Galen's in Alexandria.

In the eleventh and twelfth centuries came the heyday of the great coeducational medical school in Salerno, where men and women taught students from all over the known world and again interpreted old texts for them. Among the most popular teachers was a famous woman named Trotula, the mother of two brilliant sons and wife of Platearius, with whom she collaborated in several important volumes, compiled, doubtless, from extant remnants of Hippocrates and Galen and others to which, from their own experience, they added explanations and certain case records.

#### THE TWELFTH AND THIRTEENTH CENTURIES

In the twelfth and thirteenth centuries at least two noted women wrote medical texts; one was a German abbess named Hildegard (1098-1179), of the Rhine region, the other a Greek princess in Constantinople named Anna Comnena (1083-1148). Hildegard had been well educated in medicine by her aunt and others in a famous German abbey. She became

the friend and adviser of Saint Bernard and of three popes and two kings and was for many years the head of an abbey of her own on the Rhine. Hildegard wrote in poor Latin mixed with colloquial German. She not only treated patients so skilfully that they came to her from miles in every direction but her several medical books have been considered the best textbooks of the Middle Ages. Her botanic knowledge was phenomenal and her experimental methods of testing the value of her remedies were most advanced for the time.

Hildegard's contemporary Anna Comnena was a famous medical woman in far off Constantinople; she managed a great general hospital of a thousand beds as one of her duties during the early crusades. She was the daughter of the emperor, an expert physician, well trained by tutors. She wrote a great medical book containing many case histories, including a report of her father's last illness. She presided over the conferences of the physicians who were in the city in those years but whose names and deeds are now forgotten. Since she wrote in Greek and there was little call for translations from that language during the following centuries, her writings were forgotten but they are important medical texts, written by a medical woman.

A little later the skilled Abelard in Paris taught medicine to his beloved pupil and wife, Héloïse. He even praised her as the most intelligent woman physician and surgeon in the country. She taught many pupils and gave her life for her humble patients.

#### THE FIFTEENTH CENTURY

In the fifteenth century there were many educated women on the continent and in England studying medicine, collecting books and helping the poor and the sick. Among them was an Italian named Christine, from Pisa (1363-1431). Her mother was the daughter of the famous anatomist of the fourteenth century, Mondino, whose assistant was a young woman named

Alessandra Giliani, one of the first anatomists to inject the veins before dissections. As Mondino lectured she demonstrated the organs and tissues before his class. She died in 1326.

Christine's father was a physician and astrologer who was invited to the court of the French king as special consultant. He moved his family to Paris, where they were lodged in the royal palace, and there Christine, only a child, sat before the great library fire, curled up in a big chair browsing among the books and studying with the royal tutors. The "seven liberal arts" were the foundation of all education in those days, and medicine was included in the list.

She began writing poetry when very young, was a lover of Plato and Ovid, and became a strong feminist so soon as she read the tales in the Romance of the Rose and realized the inferior position given in them to women. She married the king's secretary, who appreciated her literary talents, and he urged her to write not only poems but essays on feminism, chivalry and pacifism. He and her father and the king all died as she was establishing her career and left Christine to support her two children and her mother and sisters by writing. This was a new role for women, and Christine's writings were very popular. She dreamed of a Utopia in which women were able to show their superiority and she produced a great work entitled *The City of Women*, in which she extolled all the great women of antiquity and then showed the glory of a city built entirely by women surrounded by a wall as high as that of Carcassonne, in which were schools and hospitals and churches, women physicians, surgeons, teachers, lawyers and preachers. She also wrote of military tactics, medicine and charity. Her admiration for Joan of Arc knew no bounds, but her own spirit failed when Joan was imprisoned and killed. She retired to a convent to practice the seven works of mercy for the sick and infirm, and showed mothers how to care for their children and how to feed their families in a wholesome way. Her only poem in those days was a eulogy on Joan of Arc in which are the well known lines

God knew well how to create great women  
Since He created thee.

Christine da Pisa was an outstanding example of the educated medical student of the fifteenth century.

#### THE SIXTEENTH CENTURY

In the sixteenth century, as has been already hinted, the famous Italian physician and Greek scholar Linacre, from the medical school of Padua, was invited to London to become one of the royal physicians and tutors at the court

of Henry VIII, among whose friends were Erasmus, Sir Thomas More and Cardinal Wolsey.

When the College of Physicians was founded, Linacre opened his house as a coeducational medical school, near St. Paul's Cathedral. We may suppose that the two daughters of Sir Thomas More were among the first pupils. Margaret More married her private medical tutor, Dr. Roper, and Margaret Giggs, her foster sister, married her tutor, Dr. Clements. Both men were physicians to King Henry and Queen Catherine. Troublesome times, nevertheless, were ahead for Sir Thomas More and his friends over the question of Henry's first divorce, and one after another of the royal advisers was imprisoned and killed. The More women soon had to use all their medical skill in treating the sick, and the two Margarets cared for Sir Thomas in prison before the headsman's ax fell. The prisons were filthy, the homes of the poor were like sties, and when the plague raged misery reigned everywhere.

Many women of the nobility, the mother of Sir Francis Bacon, for example, studied and practiced medicine. Linacre lectured at the great universities and he upheld medical women, but gradually he gave his time to the Greek language rather than to medicine. Henry kept on with his marital program but provided his daughters Mary and Elizabeth as well as his only son with medical tutors so that they might advise even the bishops as to things medical.

#### THE SEVENTEENTH CENTURY

Louyse Bourgeois le Boursier was the wife of a barber surgeon in Paris whom she had learned to assist in his operations and even to take his place in emergencies. He died young, leaving her with two children. She applied to her friend Paré for more teaching but he advised her to specialize in midwifery. He lent her his newest books and gave her many ideas as to technic. She was so apt a student that he recommended her to the queen, Marie de Medici, and she was immediately engaged as royal accoucheuse.

Louyse Bourgeois not only cared for the queen in all her seven confinements but was midwife in chief to the ladies of the court, refusing to do abortions for any woman at any price, and producing living babies where sterility or dead infants had previously been the rule. She practiced in Paris for many years and wrote the best book on obstetrics ever printed—a work which she dedicated to her daughter.<sup>1</sup> *The Rose Gar-*

1. Louyse Bourgeois's writings have a very modern ring although here and there she lapses into contemporary pseudoscience. One of her books begins "As it is not the duty of women to write books I never would have undertaken it but for the urge of the administrators of the Hôtel Dieu. . . . I have had a repugnance to the publication of my methods and observations for fear that they will be used as a short-cut to becoming a sage femme without sufficient training." Louyse also hopes no one will think her egotistic for writing her experiences and putting her advice on paper.



den of Roeslin was thus superseded and Louyse's volume went through many editions. She died in 1638, and historians call her the first really modern obstetrician. She showed great skill in manipulating versions in difficult birth, and because of her special cleanliness she lost very few patients from puerperal fever.

Louyse Bourgeois was followed by Marguerite Lehoursier du Coudray, her grand-daughter, who, together with another of Louyse's pupils, Marguerite du Tertre de la Marche, became famous teachers and supervisors of obstetrics at the Hôtel Dieu in Paris for many years. Mme. Boivin, one of their pupils, carried their traditions into the eighteenth century. Mme. Dugés and her daughter Marie Louise Dugés-Lachapelle carried the teaching still further into the early nineteenth century, when many men physicians from Europe and America studied in Paris with these famous women. They all wrote excellent textbooks which went through many editions up to 1824, quite eclipsing the works of Mauriceau and Baudelocque. To those women the Chamberlen forceps was both unnecessary and dangerous. They knew not why the use of these instruments should be followed by puerperal fever, but they discarded them. The University of Marburg bestowed an honorary M.D. on Mme. Boivin for her excellent work.

Surgery, despite the teachings of Ambroise Paré, was in the main relegated to women and quacks in Europe during the seventeenth century. They couched for cataract under any tree; they operated for stone and removed tumors wherever they found a patient. Hernias and compound fractures were everyday surgery, and it was cheaper to pay a fine than to get a license. Not until A. D. 1800 was the College of Surgeons founded in England, and surgery then began to emerge from under the authority of the physicians.

One example of an English woman of noble birth who became a capable physician and surgeon in the seventeenth century through her mother's teachings and the oversight of medical tutors was Anne Murray. About 1649 she was "wounded in love and hoped to die." She said that she "laid some hours speechlesse," then she "began to gape and bethought her of her own cordialls," and "her speritts revived." She soon married Sir James Halkett, despite her badly pock-marked face. She had four children, three of whom died in infancy. With her husband, an army officer, Lady Halkett went to the battle of Dunbar in 1650 so as to care for the wounded soldiers. She "saved sixty badly mangled men," for which the king gave her "fifty pieces of money." Her later medical career was extraordinarily successful, and patients flocked to her from all over the country. Lady Halkett was not only a very

successful surgeon and writer of medical books but a preacher and writer of religious tracts and books, twenty-one volumes in all. She died in 1699, full of honors, at a ripe old age.

Two more English women surgeons should be cited because of their excellent work. One was Elizabeth, countess of Kent, who published a popular work on physic and surgery from her own experiences in 1670. This was republished in England and translated into German and published in Germany. The other was Catherine Bowles, famous for her comparatively painless operations for hernia and stone in the bladder. There was no really painless surgery in those days, although opium and whisky were freely used. The nauseating "solvent" for stone, a remedy invented and widely advertised by a clever woman impostor, Jane Stevens, was bought by trusting sufferers at great price, and the prescription for its preparation of soap and lime and what-not was bought by parliament for an enormous sum, ostensibly for the use of the poor, but most of the patients found the treatment worse than surgery and of no actual benefit.

#### THE EIGHTEENTH CENTURY

The eighteenth century has given us the biographies of many clever medical women in every country.<sup>2</sup> Of them all, however, only one woman was mentioned in Mrs. Sarah Josepha Hale's<sup>3</sup> great encyclopedic *Woman's Record* published in America in 1853. She was Maria Delle Donne of Italy, born in 1776, a woman admired and honored by Napoleon for her remarkable obstetric work in Bologna, where she was a professor in the university. She died in 1842 and her death was recorded throughout Europe and America.

#### THE NINETEENTH CENTURY: MEDICAL EDUCATION OF WOMEN

I have shown that even before the nineteenth century many women practiced medicine in every generation with as much success as though they had had a university education, but it would have been good for both men and women to have wider training.

In 1847 Elizabeth Blackwell, who had been studying medicine privately with medical teachers, as most men studied in those years, applied for admission to nearly a dozen American medical schools, but only one, in Geneva, N. Y., was opened to her, as more or less of an experiment. This was a "regular" medical school, nonsectarian, but through no fault of hers it was promptly closed to women after Elizabeth's graduation, when various regular and irregular schools admitted women.

2. Mead, Kate C. Hurd: *A History of Women in Medicine*, Haddam, Conn., Haddam Press, 1938.

3. Hale, Sarah Josepha: *Sketches of All Distinguished Women from the Beginning till A. D. 1850*. In *Four Eras*, with Portraits, 1853.

In other countries medical education was opened to women as follows: Switzerland 1864, Paris 1867, Sweden 1870, the Netherlands 1873, Denmark 1875, Russia (temporarily) 1876, Italy (as a demonstration) 1877, London 1877, Spain 1881, Scotland 1886, Belgium 1890, Portugal 1897, Austria 1897, Germany 1900.

Although women were never actually excluded from the Italian universities if they were prepared for their courses, few did apply, and it is said that women might have been admitted to all Scandinavian medical schools after 1870 had they applied there. In Russia the government of the nineteenth century played fast and loose with women students not because they feared for the health of girls but because of the changeable political conditions in the country. Men and women nihilists were routed out of their classes at the university on slight pretext. Many of them, therefore, went to Switzerland in the sixties to study medicine, for doctors were sadly needed. In several Swiss cantons the universities were opened to women as soon as there were fitting applicants, but many of the pioneer Russian women students were among those called home by the czar in 1874 and sent to Siberia as traitors.

Even in the free land of America, however, it had been difficult for either men or women to get an adequate premedical education in the first half of the nineteenth century. In 1846 a midwifery school was opened in Boston to prepare women for obstetric work because of the "indelicacy" of having to employ men midwives in labor cases. Before 1830, on the other hand, when most of the medical schools were privately owned, one or two men gave all the courses to unprepared students (men), but as early as 1760 a New York law had been passed regulating the practice of medicine and making it imperative that a physician should be examined for a license to practice by "His Majesty's Counsel or a Judge of the Supreme Court and the King's Attorney General and the Mayor of the City or any three of them." This was only locally obeyed. Benjamin Franklin advised men to go to Edinburgh for a degree, and many rich men took his advice.

Medical education was still in confusion when Elizabeth Blackwell was admitted to the medical school in Geneva, N. Y., and it has been difficult for biographers to evaluate the lives of the then practicing American doctors according to estimates by their colleagues rather than by those of admiring patients or obituary records in newspapers. Nevertheless, the remarkable work of Kelly and Burrage<sup>4</sup> is a mine for biography hunters and saves many a long and tiresome research. Judged by the standards of this great

work a man or a woman included in the text must have been not only an outstanding doctor or credited with considerable public work or a discoverer of some new method of treatment, a sanitarian, a teacher, a remarkable surgeon or a good writer or lecturer and prominent in scientific or medical circles. Fortunately there are many medical women included in these biographies and in encyclopedias of various kinds. From such sources as well as in certain popular local histories and libraries we find the biographies of important medical women. Fortunately, academies and seminaries had already been opened to young women of eastern America by scholarly women even before the eighteen thirties, when Oberlin and Antioch colleges became coeducational. Mary Lyon founded a seminary in South Hadley, Mass., for women who wished to become teachers or missionaries, and Miss Willard's school in Troy, N. Y., and Dummer and Ipswich academies in Massachusetts and several Moravian schools had been opened for "healthy and happy Christian young women."

Railroad travel was very limited before 1850 and considered an adventurous undertaking. Ordinary journeys were made by carriage over bad roads or on horseback through long stretches of lonely country in the "far west," even to Pittsburgh; mountains were fearsome, and swollen river fords dangerous. In 1825 the first railway train was driven over a small stretch of country in England, and the train from Albany to Schenectady was an experiment in 1830. Quarantine for contagious diseases was lax before 1840, and the general mortality of all classes and all ages was high until there was effective cooperation between state boards of health and the public health service at that time.

Judged by the standards of the American Medical Association, when taken in connection with the general advance in preparatory education of women, one finds them after the eighteen fifties ready to undertake the study and practice not only of general medicine but of every special branch of medical science, so that fifty years later, when many new departments had come to be included in a medical curriculum, there was as diversified scope for women's talents as for those of men, and one notes the names of such specialists as Alice Hamilton in industrial diseases, Carroll Birch in blood dyscrasias, Florence Rena Sabin in anatomy and histology, Ellen Potter in public health, Josephine Baker in sanitary work to decrease infant mortality, Gladys Dick in the diagnosis of contagious diseases, Catharine Macfarlane, Bertha Van Hoosen and Lilian K. P. Farrar in surgery, Anna Broomall and Rachel Yarros in obstetrics, and Priscilla White in diabetes.

4. Kelly, H. A., and Burrage, W. L.: American Medical Biographies, Baltimore, Norman, Remington Company, 1920.

## MEDICAL SCHOOLS ADMITTING WOMEN

In 1900 there were 162 medical schools of all grades in the United States, but by 1935 there were only seventy-seven class A schools still in existence, so sweeping had been the work of the American Medical Association in eliminating inferior and proprietary schools while elevating the general level of medical education. Fortunately, the Women's Medical College of Pennsylvania was among the number still in existence, and most of the state universities were coeducational.

In the earlier days, when the American Medical Association was revived (in 1847), many innovations were occurring among women's organizations. The first woman's suffrage convention was held at Seneca Falls, N. Y., in 1848. Elizabeth Blackwell was then a senior at the Geneva, N. Y., Medical School, antislavery and temperance and missionary societies were swinging into line, and women were beginning to preach and to study law as well as medicine.

Elizabeth Blackwell, as has been said, was graduated in 1849 and her sister Emily in 1854, and the Woman's Medical College of Philadelphia was founded in 1850. Both of the Blackwells and many graduates of the Philadelphia and Boston schools went to Europe to study after receiving diplomas in the United States. But aids in diagnosis were rare.

Students had no microscopes, no stethoscopes, no clinical thermometers, no ideas of antisepsis or of the role of bacteria, and no personal knowledge of anesthetics for the elimination of pain during surgical operations or during labor, but the numbers of medical women increased rapidly.

In 1940 we find the following astonishing statistics taken from the United States Census by Dr. Louise Tayler-Jones<sup>5</sup> of Washington, D. C.: In 1870 the number of registered medical women was 527, in 1880 2,432, in 1890 4,557 and in 1900 7,387. Since then women have been graduated from medical schools as, roughly, 4 to 5 per cent of the men graduates; i. e., in 1905 there were 1,073 women in medical schools, or 4.1 per cent of the number of men; in 1915 there were only 592, or 4 per cent, in 1925 910, or 5 per cent and in 1935 1,077, or 4.7 per cent. Various reasons were given for these data, such as the house cleaning of medical schools by the American Medical Association—diploma mills being excluded—which reduced the number of schools from two hundred to one hundred, after the admirable survey by Abraham Flexner.

In 1937 there were only seven medical schools in the United States which did not admit women,

and only one which did not admit men except to its staff of professors.

Most colleges now require at least three years' premedical course, and more than half of the women students are college graduates—all require one year's internship before registration for practice and before taking the state or National Board examinations.

Another fact, however, is significant: Among 712 hospitals approved by the American Medical Association only 105 have internships open to women, but even there it is not always easy for a woman to secure a good rotating service, especially in surgery.

The old and worn out statement that diploma'd medical women marry and do not practice has been proved quite incorrect and may be a wishful thought of the anti-woman intern medical man; but statistics show that, although one third of the women do marry and have families, very few fail to practice.

Among the early pioneer medical men and women were many "irregulars," if judged by university standards. Undoubtedly certain "pathies" seemed reasonable to certain people. There were water cure institutions which graduated both men and women, and eclectic schools, and hydro-electro concerns, and vegetarian and Thomsonian schools, as well as popular Homeopathic colleges like that of Dr. Clemence Sophia Lozier in New York City, which was of high grade in its own pathy and which flourished in reaction against the enormous and poisonous dosage of some of the "regular" schools. In the middle of the nineteenth century, surgery was a matter of speed and luck, since "laudable pus" was expected to follow any wound, and anesthetics were still experimental; but many women soon became excellent surgeons.

Such conditions still prevailed up to the eighties, while medical women grew mentally and scientifically as rapidly as men and kept shoulder to shoulder with them in education and practice. Nor did their health suffer from their heavy work but quite the contrary happened, as Dr. Elizabeth Bass of Tulane University has recently shown, and many of the most prominent women in medical circles died of old age: Elizabeth Blackwell at 89, Emily Blackwell at 84, Elizabeth Cushier, teacher, surgeon, obstetrician, at 94, Marie Zakrzewska at 73. The British medical women were as long lived. But few medical women in any country failed to earn a good living, and many of them brought up large families, among whom might be mentioned Hannah Longshore, Mary Frame Thomas, Mrs. Dolley, Mrs. De Hart and Madame Lozier in America as well as Elizabeth Garrett Anderson in England. They raised their families, practiced medicine most successfully, did magnificent public service, and died at as ripe an old age as the unmarried women doctors.

5. Jones, Louise Tayler: *Medicine as a Field for Women*, J. Assn. of University Women, 1938.

## BIOGRAPHIC NOTES

Fortunately it is becoming somewhat easier, as the years roll on, to collect the biographic histories of medical women in various countries. Beginning with Glances and Glimpses, or the autobiography of Harriot K. Hunt of Boston, early in the nineteenth century, one turns to Elizabeth Blackwell's autobiography and to that of Marie Zakrzewska, compiled from her own diaries by Dr. Agnes Vietor, and to Mary Putnam-Jacobi's life and works prepared by her niece, and to Emily Blackwell's career by Dr. Annie Daniel, and Ann Preston's life and that of other early teachers in Philadelphia as written by the successive deans of the Women's Medical College of Pennsylvania, and many others in every country, biographies which add immeasurably to the historical value of medical history though they have been overlooked by men historians. Naturally there are still many lacunae in every state and country which must be filled by willing workers.

We are indebted to Dr. Victor Robinson for publishing biographies and a general history of medical women, in the *Medical Review of Reviews* and to Dr. F. C. Waite of Western Reserve University for his articles on the early medical schools of the United States, including the biographies of the earliest women members of the early coeducational schools, and to the *Medical Woman's Journal* and the publications of the medical women's associations in America and Europe which have appeared since the founding of national associations of medical women during the war of 1914-1918 and subsequently.

It is fortunate that men and women differ in their outlook on life but unfortunate that women should still find it difficult to win adequate recognition for their talents and to obtain adequate internships. Opportunely Bellevue Hospital in New York now has thirty-two women interns on its staff and the Philadelphia General Hospital has nearly as many more, while the hospitals for women in several of our large cities also take many women interns; but there is in fact a serious shortage of adequate positions for women interns, since they as well as men must have rotating hospital service in class A hospitals before obtaining license to practice, but, as hospitals are supported by the public, women should be appointed to hospital posts on the same terms as are men, entirely without regard to sex, especially in states which demand internships before taking state examinations. Lately, however, has come an appeal from one Louisiana maternity hospital for women applicants who wish to specialize in obstetrics. Many small hospitals approved by the American Medical Association are said not to have had women applicants although offering internships to them.

During the existence of the New York Infirmary Medical School for Women and its thirty years of teaching it sent forth hundreds of able women as well trained as any men or women in the world.<sup>6</sup> Its graduates have been successful in practice in foreign fields as well as at home, many have become famous surgeons and x-ray specialists, and others have made important laboratory investigations in cancer, bacteriology and public health work. Its first class was graduated in 1870 by the Blackwells, and a class went out each year until 1899, when it united with the Cornell University Medical College.

It is evident, therefore, that there can be no differentiation between the sexes in medical study or practice and that neither in the United States nor in England was any distinction thought necessary by the founders of the medical schools for women. The old Boston (Gregory) medical school for women was united with Boston University after about thirty years of teaching, and the Chicago school was united with the Northwestern University eventually, not because of failures in their students or inability to balance their budgets but because it is economically beneficial to combine the expensive paraphernalia of buildings, equipment and staff in one or more large institutions.

The Woman's Medical College of Philadelphia and the London, Royal Free Hospital School of Medicine for Women, however, have continued with their original purpose in order to give opportunity for women as professors and more intensive education for women in gynecology, obstetrics and surgery than they could obtain in a man's college; they should also insure a solidarity among medical women like that which has been held by men since the earliest times. In every case, however, medical women have been assisted by the noblest of medical men in attaining their aims and in founding medical schools and hospitals for their needs as well as in the practice of medicine.

Among the first coeducational medical schools was the University of Michigan Medical School, which graduated its first medical woman, Dr. Amanda Sanford, in 1869. Since then it has graduated hundreds of women of whom the university has been proud.<sup>7</sup>

WOMAN FOUNDERS OF HOSPITALS  
AND TEACHERS

Many of the early woman graduates of the medical schools in the United States founded hospitals or dispensaries for women and children soon after their own graduation. The New England Hospital for Women and Children in Boston was founded by Marie Zakrzewska,

6. Daniel, Annie S.: A Cautious Experiment, *M. Woman's J.* 46: 125 (May) 1939 and subsequent issues.

7. Selman, Bertha: Medical Women in Michigan, *M. Woman's Quart.*, 1910.

M.D., Cleveland, 1856; the New York Infirmary by Elizabeth Blackwell, M.D., Geneva, 1849, and her sister Emily, M.D., Cleveland, 1854; the Detroit Woman's Hospital and Foundling Institute by Sarah A. Gertrude Banks, M.D., University of Michigan Medical School, 1873; the Woman's Hospital in Philadelphia by Ann Preston, M.D., Woman's Medical College of Pennsylvania, 1852; the San Francisco Hospital for Women and Children by Dr. Charlotte Blake Brown, who had been an intern at the New England Hospital in the early seventies.

Such a list could be shown in England and Scotland, where Elizabeth Garrett-Anderson's large hospital in London grew out of her dispensary opened in 1864. Sophia Jex Blake's hospital and medical school was founded in the early eighties in Edinburgh because of the demands for the medical education of women in Scotland. The Royal Free Hospital in London, connected with the medical school for women, became a teaching hospital in 1877 as the result of the energetic work of the women pioneers and their friends, and it still grows.

In the nineteen thirties one finds here and there successful women doctors teaching in coeducational medical schools, few, however, having "full chairs." At the same time there were sixty-eight women on the staff of the Woman's Medical College of Pennsylvania, twelve being full professors in surgery, obstetrics, gynecology or pediatrics. The graduates of this college have seldom failed to fill hospital as well as teaching positions with honor, and they have had but few failures in examinations for state licenses or internships.

The governors of Old Blockley Hospital in Philadelphia have always been fair to women candidates. In 1883 Dr. Pauline Root was the first woman to win an internship there, and she had a most valuable training preparatory to entering missionary work in the south of India. Even in the forties and early fifties Elizabeth Blackwell and Sarah Adamson (Dolley) were given the privileges of the obstetric wards at Blockley.

In New York City in the late sixties Dr. Emily Blackwell and Dr. Sophia Lozier led their students to the wards and lectures at Bellevue Hospital, where, many years later, Dr. Emily Dunning (Barringer) of the Infirmary School was the first woman intern and ambulance surgeon.

When Mary Putnam (Jacobi) returned from Paris in 1871 with her French diploma she was at once accepted as visiting physician at Mount Sinai Hospital, which has never closed its doors to women.<sup>8</sup>

8. Unfortunately, no woman was appointed to the early staff of the Woman's Hospital in New York City, although women had been instrumental in founding it and had been given a promise from Dr. Marion Sims, its surgeon, that a medical woman would be resident physician there. Various excuses failed to soften the blow to women doctors or their cause because of his failure to keep his promise.

Beginning with the founding of women's hospitals by woman doctors the training of nurses has been continuous and valuable. In the Philadelphia Woman's Hospital, connected with the medical school, Dr. Ann Preston and Dr. Emmeline Cleveland in 1863 organized a regular course of lectures and practice for woman nurses. This was continued by Dr. Edwin B. Fussell and Dr. Mary Scarlett-Dixon, and student nurses received certificates after severe examinations. It has had a steady growth.

The nursing school in the New England Hospital, Boston, under Dr. Susan Dimock, Marie Zakrzewska and others was the first to be chartered. From this school Linda Richards in 1872 received the first diploma ever granted a nurse in this country. She eventually organized several other schools, and Yale and Bellevue soon followed, bringing in their train those of Dr. Gertrude Banks in Detroit and Dr. Charlotte Brown in San Francisco.

Woman student pioneers in coeducational medical schools have generally won prizes or prize positions for interns by competitive examinations. Mary Elizabeth Bates of Colorado won the first position as intern at the Cook County Hospital in Chicago, but she was subjected to many annoyances on that account. Edith Pechey Phipson, an extramural student at Edinburgh University, 1869-1872, won a coveted chemistry prize but it was not awarded to her. Woman doctors in those days were often subjected to impolite attentions by the public in general but gradually they were accepted simply as "queer." This attitude has been followed by one of indifference, which has perhaps been harder to overcome and is also vanishing.

Woman surgeons have perhaps had the hardest struggle for recognition. Among the pioneer woman surgeons in America was Elizabeth Cushier, who performed major operations at the New York Infirmary for twenty-five years with as great success as was achieved by Marion Sims and Emmett and other noted men. Elizabeth Keller and Fanny Berlin operated at the New England Hospital in the eighties, and their laparotomies gave them great credit. Charlotte Blake-Brown in San Francisco performed the first successful ovariectomy on the Pacific Coast. Hannah Thompson in Chicago operated for many years as cleverly as did the men of the largest hospitals. Anna Broomwall and Hannah Croasdale followed Emmeline Cleveland as surgeons at the Woman's Hospital in Philadelphia without the least adverse criticism.

Women as medical lecturers on physiology and hygiene have been generally accepted by the public from their earliest years without opposition until, following Dr. Hannah Stone and Dr. Valeria Parker, they began to teach sex hygiene and to point out the possibilities

and advantages of conception control and the prevention of venereal diseases. This has brought them many staunch defenders as well as opponents among the medical men. Fortunately the subject is now bravely furthered in *Hygeia* by the American Medical Association's editorial staff and by noted men such as Drs. Parran, Flexner, Fishbein, Robert Latou Dickinson and C.-E. A. Winslow.

#### WOMAN AUTHORS AND WOMEN IN IMPORTANT POSITIONS

Many medical women have written successful books on hygiene and public health, beginning with those by Dr. Harriot K. Hunt of Boston, Elizabeth Blackwell of New York, Elizabeth Garrett and Sophia Jex Blake of London and others leading up to those of Dr. Belle Wood-Comstock of California, Dr. Lena Sadler of Chicago, Dr. Josephine Baker of New York, Dr. Lulu Hunt Peters, Dr. Josephine Jackson and others.

Several women have had important positions as heads of city, county or state departments of health, among whom the earliest was Dr. Mary Frame Thomas, city physician in an Indiana town in the sixties, Dr. Mary R. Butin of Madera County, Calif., head of the county department of health in 1902-1913, and Dr. Esther Pohl Lovejoy, chief of the State Board of Health of Oregon, 1907-1909. Many other medical women have filled similar important position, among whom may be mentioned Dr. Ellen Potter in New Jersey and Dr. Martha Tracy and Dr. Mary Riggs Noble in Pennsylvania.

Unfortunately, few medical women have had the honor of membership in the House of Delegates of the American Medical Association, although many have been officers of their state and county associations. This is regrettable since the double point of view of males and females provides for the elimination of many errors in judgment. Dr. Sarah Hackett Stevenson caused no little consternation when the Illinois State Medical Society sent her as a delegate to the annual session of the Association in Philadelphia in 1876, but she was accepted politely and apparently did no harm! Since then, however, she has had few followers. Among the fortunate few are Drs. Frances Rutherford and Marie E. Greene of Michigan, Dr. Martha Welpton and Dr. Mary R. Butin of California and Dr. Emily Dunning Barringer of New York, but woman members of the Association feel that they should be continuously represented among the delegates, since there is no longer a question of sex in medicine and minorities should always be able to express their views in any association doing business

of any kind. This was the theme of an address given by the President of the Association, Dr. Ray Lyman Wilbur, in 1923 at the San Francisco meeting of the Medical Women's National Association. Unfortunately, however, medical women are not as a whole politically minded or insistent on their privileges even in minorities.

Since the organization of the International Association of Medical Women in 1919 it has been found all over the world that woman doctors have the same high ideals, the same kind of mentality, the same general objectives, unselfishly working to reduce physical suffering and lessen morbidity and mortality and therefore to eliminate crime and misery. Better still, they are working in similar ways and with similar instruments. They understand one another no matter what language they talk, for the education of women, like that of medical men, is the same the world over.

There is no place on the globe so hot, so cold, so dreary, so miasmatic, where women doctors have not worked as hard and intelligently as men. Women doctors are found among the starving populations in China, the fanatical castes of India, the aborigines of Central Africa and the unlettered natives of South America as well as in the slums of the great cities of the world.

Through the American Women's Hospitals' Committee of the National Medical Women's Association, financial aid and medical personnel have been sent to all the warring countries during war and reconstruction. Woman doctors have traveled with ambulances and dispensaries and opened clinics or temporary hospitals wherever the ravages of war have made such help necessary. At the present time (midsummer of 1940) medical women are on the battlefields in the warring countries and are being materially aided by the medical women of the United States and Great Britain.

In several of the Southeastern states medical women and nurses are working under the American Women's Hospitals' Committee of the Association of American Medical Women to improve the health of the mountain whites. The personnel is maintained in conjunction with the boards of health of the contiguous counties to provide prematernity and child welfare care, as well as good obstetrics, in localities far from the city hospitals, and also to provide proper dietaries for tuberculous invalids and to aid in the elimination of hookworm and beriberi, carrying on the work by means of traveling dispensaries and clinics, teaching home nursing and first aid, and doing whatever is needed to improve the health and working efficiency of these neglected white people. Thus the field of service for medical women continually widens.



## CONCLUSION

Finally, I must close this tightly compressed article hoping that the vision of some medical students has been sharpened to look still further into the detailed history of medical women and also to preserve the records of the quiet and self-effacing women in the profession who are content to do careful and scientific work for their patients without the blare of trumpets. Surgeons like Dr. Gertrude Herzfelt in Edinburgh and Louisa Martindale in London, obstetricians like Dr. Joan Rose in Scotland and

Dame Louisa MacIlroy in England have their prototypes in the large cities of the United States. Women should be proud to belong to such a noble profession, and unite to uphold it with all their might, while realizing that in medicine as in music the pauses and silent spaces are as important for them as the trumpet notes, but insisting on the generosity of the majority to the minority of the medical practitioners, and by union of well trained women to prove that it is quality, not numbers, that counts.

## British Students Carry on After Bombing of St. Thomas's Medical School

St. Thomas's Hospital Medical School in London, one of the most famous medical schools in the world, has been evacuated following several attacks by German bombers. New arrangements were quickly made, however, for the students to carry on their studies elsewhere. The preclinical subjects and pathology are now being taught in Godalming, where the premises of a girls' school and other buildings have been taken over for teaching and billeting purposes. The senior students are centered at Guildford, while the other clinical courses are centered in several hospitals throughout the sector.

In the December *St. Thomas's Hospital Gazette*, students write of the experience. Several students who at first went to the roof of the hospital to watch some thirty German bombers, beat a hasty retreat when a large whistling bomb fell within a mile of the hospital. They slept in the basement that night and in the early hours of the morning were awakened by a terrific crash. Hurriedly they made their way to the corridor to be met by a wall of smoke, dust and fumes. A block of the hospital had been hit. They stood aghast at the damage for a second, then organized a searching party and went through the building to remove from the rubbish the sick and invalid. When daylight came it was revealed in the shambles that none of the patients had been hurt, although all in Adelaide had to be removed to the shelter of Edward. A nurse and a masseuse were still buried among the ruins and believed to be still alive. Rescue squads were trying to save them. The ward patients were carried downstairs in their beds to the basement for safety. Can anyone imagine, they ask, how much staying power it takes to carry a heavy man downstairs in his bed and insure that his suprapubic drainage is intact when he gets to the bottom? All other patients were evacuated the next day to their homes if well enough or to the sector. Although they were tired when this task was done, the cheerfulness of the sisters and nursing

staff and their constant activity to help others were incredible.

The medical students had to find other quarters for the night and on the following day were assigned quarters in the roentgen ray department, where they carried their mattresses. A piano was put in the corridor at the entrance to the department, a sing-song was organized and an informal party enjoyed until 10:30, when all went to bed. In the early hours of the next morning another terrific crash occurred and debris came clear through the hospital to the basement, causing some casualties and necessitating many readjustments. The students believed that their "mattress barriers" on this occasion saved their lives. As the hospital accommodations were now much reduced, and it would be better, some of the students went home.

A few days later a large bomb hit College Hospital and went clear through to the basement before exploding, causing three deaths. Never before have medical students and physicians been able to see the real worth of the Nightingale training and the women from whom nurses are drawn. Bombed out, blasted from their quarters, and some losing all they had, the sisters and nurses kept on working to make others comfortable. The hospital was falling in parts about their eyes.

Accommodations for the first, second and third year students were now found at a new location in Surrey, where they were quickly able to settle down to work in dormitories (those of a former girls' school) and with reading and dining rooms and some of the atmosphere of a club. Some of the students lived in private billets. The various departments were housed here and there, the physiology and pathology sections in stables, which is not as bad as it sounds. The anatomy department acquired a squash court to be used for dissections. Here specimens for a time were at the mercy of the elements, but plans went forward quickly for the building of huts for this department. The

biology, physics and chemistry departments had part time use of the laboratories of a neighboring public school, and their clinical teachers come down to lecture and take the students for ward rounds twice a week elsewhere in the sector. They receive visits from Mr. Robb, who talks about surgery, Dr. Petch, who talks about medicine, Dr. Thomson, who takes them for ward rounds, and Dr. Bamforth, who comes frequently to talk about the blood.

The other student activities, they write, continue much as they did at St. Thomas's. There is a vigorous soccer team and a rugger team. On the whole, they are having a remarkably good time. Other students write of having arrived at St. Thomas's after a third bomb had registered, making it probably necessary that they should have to look to the sector until the war was over. Students who were fortunate enough to be doing gynecology came out to the country base in the sector, where they were welcomed as men rescued from the front line trenches, Mrs. Milligan refreshing them with sherry and tea and Mr. Wyatt having billets awaiting them so that their medical lectures and other classes began at once at the Warren Road hutments. The country club even admitted some of them as special members, and the golf club halved its fees. More students arrived from time to time until there were one hundred altogether. An empty shop was used as a lecture room, and the volunteers who ran it probably enjoyed the lectures, which they heard through the partition as they prepared lunch.

A Red Cross room in the county hospital was lent for classes in medicine and surgery, and the courses in the special departments and in gynecology were held at the county hospital and at Warren Road. A second vacant shop was acquired to serve as both library and lecture room. They were not prevented from having tea with the 4 o'clock classes, even though the teachers might occasionally be unable to reach the class. Thanks to the energy of all the neighbors, they had a fair chance of carrying on their work and of dealing with imminent examinations. The students feel that much praise is due those responsible for the hospital arrangement and the billeting scheme under these conditions. Their only criticism might be that perhaps a little more of their time should be allowed in the outpatient department.

Some members of the teaching staff—four surgeons and nine physicians—find that the new surroundings offer many of the advantages of London plus the benefits of living in the country. They share their courses, including ward rounds, lectures on therapeutics and a weekly pathology drive, while operations are performed every other day. Surgical cases are numerous, but a medical case is a rarity. They have partial freedom of the M. O.'s house, where they gather

as they did at St. Thomas's House, and they are becoming most virile here where Hitler seems little more than a buzz in the sky.

The trauma unit has the largest clinic in the hospital. Instruction in traumatic surgery is given at all times of the day and night. Different members of the staff react to the presence of the students in different ways, most of them not unfavorably. The students find inevitably "in the excellent and enthusiastic teaching" similarity and contrasts with the former days at St. Thomas's.

Another student writes that six of them arrived at the hospital in the sector to act as paid members of a mobile ambulance unit for one month, consisting of a doctor, six nurses, two male attendants and two vans provided by the American Red Cross. They were on call to be immediately available in pairs for twenty-four hours at a time. Most of their days were given to normal hospital routine, attending clinics, operations and necropsies. Their only criticism was the exceeding thinness of the roofs above them and the want of a tin hat for each of them. The sleeping quarters for this group was a problem, as they did not fancy living on the first floor. One night their room was shared with a corpse, which they put up with; but, when more of them came, four of the students were crowded out and they returned to Surrey. The other two remained to deliver any available babies and to hope for signs of activity by their ambulance.

The *Gazette* adds that the whole school owes a tremendous debt to the school authorities for the speed and skill with which arrangements for carrying out instructions and medical care were completed, a process which has been greatly aided by the kindly cooperation of the medical officer of health for Surrey and his staff and the various medical superintendents.

---

*Delicious Moment.*—One of the most exciting moments in the medical student's career is that in which, with the examinations in anatomy and physiology just behind him, he first enters the wards of a hospital. Now, after two or three years of apparently getting nowhere, he feels that he has at last got his foot upon the good hard road of medicine. He sallies forth into the town and buys a stethoscope—delicious moment! He hurries home and then, withdrawing to his room, tremulously applies the instrument to his chest. Cavernous, incomprehensible rumblings meet his ear. This—will one ever be able to make sense of this? Is this poor thing the long-awaited voice of professional destiny? The instant doubt is quick forgotten; the next adventure hurries on; in the morning, magnificently armed with the seal and emblem of his trade, he takes his place at the bedside—his first patient before him, his mentor gazing at him across the bed. . . . But, as the time goes by, the boundaries of medicine's cultivated lands force themselves upon the initiate's attention. Beyond them he sees the vast unbroken territories in which disease runs wild.—Bateman, Donald: Berkeley Moynihan—Surgeon, New York, Macmillan Company, 1940.

## Digest and Reviews

### THE SELECTION OF MEDICAL STUDENTS AT MINNESOTA

*Abridgment of an article by Dr. C. D. Creevy, assistant dean, University of Minnesota Medical School, published in the Bulletin of the Minnesota Medical Foundation, November 1940.*

The requirements for admission to the medical school have been revised extensively in recent years. In 1937 the executive faculty increased the amount of premedical work from two years to three, and the Admissions Committee undertook a program intended to insure the selection of students who, in addition to being capable scholastically, had shown evidence of good personality, character and adaptability to the study and practice of medicine.

To insure impartiality in interpreting premedical grades, a factor was evolved for each college which sends students to the medical school. It was computed by determining the average number of honor points per credit hour obtained in the medical school by a group of students from the college concerned. This figure was divided by the average number of honor points per credit hour earned by the same students in their premedical work. The factor ranges from 0.561 to 0.914 for various colleges. The honor point average of an applicant is multiplied by the factor for his college in determining his premedical grades. Thus inequalities due to a tendency of one college to give high grades and of another to be severe are equalized on the basis of actual performance in the medical school. Prior to this time applicants had been required to take the Moss and Minnesota medical aptitude tests to determine their ability to reason along lines thought to be necessary in the study and practice of medicine. To these were added the Strong Vocational Interest and Sophomore Culture tests.

The former is intended to indicate the fields in which the applicant's chief interests lie and the latter to assess his fund of general information. If serious deficiencies are uncovered by the latter test, the applicant may be advised to take more college work.

To learn something of the applicant's personality, "rating sheets" are sent to his high school principal, his family physician and the president of the college which he attended. If

serious personality defects are suggested by these reports, or if sufficient data cannot be obtained, the applicant is called in for a personal interview with two members of the Admissions Committee.

Finally, the applicant must be examined at the University Health Service to make certain that he has no diseases which would make him unfit for the study of medicine.

This program has not been in effect long enough to determine whether it is resulting in the selection of better medical students and in the elimination of the unfit, since the first class so selected is now in its senior year. This class consisted originally of 107 members, of whom five dropped out permanently without failing and ten dropped out for a year while in good scholastic standing. Twenty-one (19.6 per cent) failed in the freshman comprehensive examinations, but fifteen passed on the second trial, while six were dropped from school for a second failure; 8.3 per cent failed in the sophomore comprehensives, all but one of these passing at the second trial; 5.2 per cent failed in the junior examinations. Seventy-five of the original 107 are now in the senior class. This is better than the average of 390 students taking each of these examinations in 1935, 1936 and 1937, in which the failures were 24, 15 and 13 per cent, respectively. Because of the small number of students admitted under the present régime, this is inconclusive though hopeful.

The freshman class of 1940-1941 consists of 114 members, 102 of them residents of Minnesota. Ten are women, five of them daughters of physicians; eighteen are physicians' sons. Forty-three had an average of B or better in their premedical work. The whole class had an average of 1.88 honor points per credit hour (B minus) in college.

Dr. Edward Trudeau, ill with tuberculosis, went to the Adirondack Mountains in 1873 to spend his last days. He improved and became convinced that with rest and fresh air he had found a method of treatment of this disease. He established there what has become the famous Trudeau Sanatorium at Saranac Lake, N. Y., and so began the sanatorium treatment of tuberculosis in America.

### DO YOU KNOW WHAT PHYSICIAN—

1. Was the greatest philosopher of his day in England?
2. Was the first of the great American philosophers?

3. Is said to have been directly responsible for the surrender of Santiago de Cuba during the Spanish-American War, July 17, 1898?

*The answers are on page 352*

## Medical College News

*Medical schools, hospitals and individuals will confer a favor by sending to these headquarters original contributions, reviews and news items for consideration for publication in the Student Section.*

### A Medical Student at Seventy

Henry Franklin Cutler was born in 1862 in Greenwich, Mass. He graduated from Amherst College, took postgraduate work in Paris, Geneva and Berlin and was instructor in languages at the State Normal School, Westchester, Pa., in 1889 and 1890. Then for nearly forty years he was principal of Mount Hermon Boys' School in Massachusetts. He retired at the age of 70 and started on a trip around the world, still imbued with his boyhood ambition to be a physician. In Paris, he decided to matriculate in a medical school. In July 1940, in his seventy-ninth year, according to the Mount Hermon Alumni News, the University of Vienna officially announced that he was "promoted to the degree of Doctor of Medicine . . . at noon in the hall of the university." Mount Hermon Boys' School plans to have Dr. and Mrs. Cutler as their guests of honor next June when the school celebrates its sixtieth birthday.

### Scholarships for Tufts Freshmen

The Charles Hayden Foundation has awarded a grant of \$10,000 to Tufts College Medical School, Boston, to be used for scholarships for selected members of the entering class next fall. Following the regular plan of the Charles Hayden Memorial Scholarships in other institutions, a portion of this will be used for outright scholarships during the first year of medical study. The remainder will be held as a special loan fund to be used in upper class years by those who held Hayden scholarships during the first year. Dr. Leonard Carmichael, president of Tufts College, in announcing the gift hailed it as a definite benefit to able and worthy young men who might otherwise be debarred from entering the medical profession. Dr. Cadis Phipps, professor of medicine at Tufts College Medical School, will serve as chairman of the committee administering the scholarship grants.

### Outpatient Department Banquets

Eight years ago Dr. Connie M. Guion originated at the old New York Hospital at Cornell University Medical College, New York, monthly outpatient department banquets at which some practical medical topic was to be discussed by a guest speaker and following which the lecture was to be open for discussion. At the December outpatient department banquet, the address was given by Dr. Soma Weiss, physician in chief of the Peter Bent Brigham Hospital, Boston, and professor of medicine at Harvard Medical School. Dr. Weiss's subject was "Spells of Unconsciousness in Medical and Surgical Practice," and as he graduated from Cornell in 1923 many of his former colleagues were in the audience. The paper was discussed by Dr. Harold G. Wolff of the department of medicine of Cornell and by Dr. William Andrus, who referred to its surgical implications, and by Joseph Hinsey, Ph.D., professor of anatomy.

### The Hamman Society at Western Reserve

At the meeting of the Hamman Society of the present school year, Oct. 14, 1940, Western Reserve University Medical School, Cleveland, Elmore R. McNeal '41 presented a paper on the diagnostic value of spinal fluid, and Paul F. Cooper '41 presented a case for diagnosis which was discussed by Edward S. Humel '41. At the November 11 meeting the program consisted of a debate

between Austin S. Weisberger '41 and Walter A. Hoyt Jr. '41 on sulfapyridine versus sulfathiazole in the treatment of lobar pneumonia. Charles W. Stertzbach '41 presented a surgical diagnostic problem. The president of the Hamman Society for this year is John C. Cutler '41, the vice president Paul F. Cooper '41 and the secretary-treasurer Elmore R. McNeal '41.

### Noontime Radio Concerts at Illinois

A year ago the *Illini Scope* presented to the University of Illinois School of Medicine in Chicago a radio with which to provide noontime concerts given in room 106 for the purpose of recreation and enjoyment by the students. The interest of these periods has grown and through the efforts of William H. Welker, Ph.D., and Tom S. Jones, the well known medical artist, a new radio-phonograph has been presented to the school by the medical faculty. This instrument offers superlative reproduction. Daily notices of the programs for these concerts are posted on the bulletin board.

### Mrs. Joseph Goldberger Addresses Texas Students

Mrs. Joseph Goldberger addressed the students of the University of Texas Faculty of Medicine, Galveston, Dec. 19, 1940 on the subject "The Adventurous Dr. Goldberger," her husband, who won fame for research on the cause and prevention of pellagra. Mrs. Goldberger was a valuable assistant to her husband in his scientific experiments. Our correspondent writes that on the occasion of this address her cheerful personality and delightful informality won the praise of the entire school. Other guests who addressed the students recently were Dr. George M. Piersol, professor of medicine of the Graduate School of Medicine, University of Pennsylvania; Dr. Harvey B. Stone, associate professor of surgery, Johns Hopkins University School of Medicine, Baltimore, and Dr. Milton B. Cohen, director of the Hay Fever and Allergy Foundation, Cleveland.

### Woman's Medical College

Dr. Chevalier Jackson, president of the Woman's Medical College, Philadelphia, introduced the newly appointed acting dean, Dr. Margaret D. Craighill, at the opening of the ninety-first annual session of the college, September 18. Dr. Francis R. Packard gave an address on "The Colonial Hospital." The enrollment at the school is 115 students, including forty-one in the freshman class.

The following students were awarded scholarships:

<b>First Year:</b>	<b>Third Year:</b>
Dorothy Macy	Judith Dudley Smith
Caroline Butchko	Louise Mildred Dantuono
Leonore Alina J. R. Bajda	Eleanor Anne Soltau
Margaret June Reed	Helen Teresa Metz
Johanna Elizabeth Lund	
<b>Second Year:</b>	<b>Fourth Year:</b>
Grace Rebecca Nachod	Badona L. Levinson
Sister Barbara Taggart	Dorothy May Brand
	Katharine R. Guest
	Beatrice Pearlstone
	Jane Marshall Leibfried

Dr. Emily Dunning Barringer, president-elect of the American Medical Women's Association and now the only woman member of the House of Delegates of the American Medical Association, addressed the junior class of Woman's Medical College of Pennsylvania

at Philadelphia, November 15, on "The Modern Treatment of Gonorrhea." At the observation of Pan American Health Day, December 2, Dr. Damaso de Rivas, assistant professor of parasitology at the University of Pennsylvania, addressed the students on malaria control, and five students from Puerto Rico and the Canal Zone gave brief talks on local health problems in their countries.

#### Christmas Party at Oklahoma

The fourth annual Christmas party at the University of Oklahoma School of Medicine, Oklahoma City, was held in the auditorium of the school, December 19, with the entire student body present. The arrangements were under the direction of the junior class, with Mr. Henry J. Freede as chairman. The various classes provided a program of music and other entertainment. The Christmas tree and trimmings were later given to the State University and Crippled Children's Hospital.

#### Joint Meeting at Loyola

The Volini Medical Society, the Moorhead Surgical Seminar and the Lambda Rho Roentgenologic Society of Loyola University School of Medicine, Chicago, met in joint session November 28. Two senior students presented papers: James O'Neil on "Technics of Direct Blood Transfusions" and Matthew Boylan Jr. on "Technics of Indirect Blood Transfusions." Movies illustrating methods of transfusion were shown. The secretary announced the appointment of Dr. Herman F. De Feo as moderator of the Volini Society to succeed Dr. Gertrude M. Engbring.

#### New Buildings at University of Kansas

A new four story clinic building costing \$225,000 and containing eighty-five examining and demonstration rooms, an auditorium seating 300 persons and a kitchen to supply the University of Kansas Hospitals has been occupied at the University of Kansas School of Medicine, Kansas City. This building furnishes about three times as much space as the old dispensary, which is being removed from the campus, and along with the Children's Hospital, the Hixon Laboratory for Medical Research and the ward for Negro patients, all opened in the last two years, comprises a plant costing about \$2,000,000.

#### Student Research Club at Illinois

At the first meeting of the year of the Student Research Club, the present status of sulfathiazole was discussed. The club meets every second Friday at 2:30 p. m. Its object is to stimulate student research, to suggest problems of importance, and to aid in the distribution and coordination of equipment. The president of the Student Research Club this year is Robert L. Grissom '41 and the faculty adviser is Dr. George E. Wakerlin.

#### Recreation Program at Georgia

One feature of the student recreation program at the University of Georgia School of Medicine, Augusta, is an informal concert of classical and semiclassical music played at various times between classes in the college auditorium, arranged through the efforts of Dr. Everett S. Sanderson of the department of bacteriology and public health. The recreation program is sponsored by the dean, Dr. G. Lombard Kelly. Three of these concerts have been held. The junior class for the last several Tuesday evenings has sponsored a series of movies demonstrating obstetric technic and procedures. Almost the entire student body has

attended these movies. The local chapter of Alpha Kappa Kappa fraternity entertained the majority of the student body and many of the faculty members at a Christmas dance, Dec. 20, 1940.

#### The Cook County Intern Examination

The results of the recent Cook County Hospital intern examinations showed, according to the *Illini Scope*, December, 1940, that the highest average grade (89.896) was that of Burton J. Soboroff, a Northwestern student; the second highest average was that of Jerome Solomon of Illinois, with an average of 88.9, and the third was Esther Pizer of Illinois, with an average of 88.396.

#### Grand Presiding Senior Emeritus

Dr. Irvin Abell, of Louisville, Ky., now chairman of the Committee on Medical Preparedness of the American Medical Association, was presented with a diamond pin and received the title of Grand Presiding Senior Emeritus during the annual meeting of the Phi Chi medical fraternity at Louisville, Dec. 26-28, 1940. Among the other distinguished guests on the program were Dr. Eben J. Carey, dean of Marquette University School of Medicine, Milwaukee, and editor of the *Phi Chi Quarterly*, and Dr. Albert F. Saunders, of Valdosta, Ga.

#### Symposium on Tuberculosis

The chapter of Alpha Kappa Kappa at Long Island College of Medicine, Brooklyn, sponsored a symposium on pulmonary tuberculosis, November 28, to which all students of the college, the faculty and members of the hospital staff were invited. The speakers were Dr. Elberton J. Tiffany, assistant professor of bacteriology; Dr. Alfred P. Ingegno, instructor in medicine, who discussed tuberculosis as it affects nurses and medical students; Dr. Emanuel Mendelson, assistant clinical professor of radiology; Dr. Tasker Howard, professor of medicine, and Dr. Lee D. Van Antwerp, of Undercliff, Meriden State Tuberculosis Sanatorium, Meriden, Conn. A moving picture entitled "First Stage Thoracoplasty" was shown, and after the meeting refreshments were served at Donnellon House.

#### New A. O. A. Chapter at Medical College of Virginia

The Brown-Séquard Society, honor medical organization at the Medical College of Virginia, was formally made a chapter of the national honor medical society, Alpha Omega Alpha, at appropriate ceremonies December 4, at which Dr. Walter L. Bierring, national president of the fraternity, conferred the charter on the local group. The Brown-Séquard Society was organized at the Medical College of Virginia in 1931 and A. O. A. was organized at the University of Illinois College of Medicine, Chicago, in 1902. This national honorary society, which has chapters in many medical schools, seeks to promote scholarships and to encourage high standards among medical students and graduates. Dr. Josiah J. Moore, Chicago, national secretary of A. O. A., presented keys and certificates to the following local chapter members: Dr. Frank L. Apperly, professor of pathology; Dr. Claude C. Coleman, professor of neurosurgery; Dr. Harvey B. Haag, professor of pharmacology; Dr. W. B. Porter, professor of medicine; Dr. Lee E. Sutton Jr., professor of clinical obstetrics, and the following senior students: Herbert C. Allen Jr. '41 of Richmond; William E. Daner '41 of Paden City, W. Va.; George A. Stewart Jr. '41 of Norfolk, and Adney K. Sutphin '41 of Beckley, W. Va.

W. T. Sanger, L.L.D., president of the college, presided at the ceremonies. Dr. Sutton, the dean, accepted a charter on behalf of the school and Dr. Porter gave an

address. The banquet was attended by Major General Merritte W. Ireland, U. S. Army, retired, former surgeon general of the Army and president of the National Board of Medical Examiners; Dr. Hugh S. Cummings, former surgeon general of the U. S. Public Health Service and now director of the Pan American Sanitary Bureau, Washington, D. C.; Dr. Hugh H. Trout, Roanoke, surgeon and past president of the Medical Society of Virginia; Dr. J. Shelton Horsley, Richmond; Dr. Harvey E. Jordan, dean, University of Virginia Medical School, and many others.

#### Wisconsin State Board Questions

The following questions were given by the Wisconsin State Board of Examiners at the examination in Milwaukee, June 24, 1940:

##### OBSTETRICS AND GYNECOLOGY

1. Give signs of separation of the placenta in the third stage of labor.
2. How is postpartum hemorrhage prevented? How treated?
3. Discuss and give treatment of nausea and vomiting in early pregnancy.
4. Describe measures employed in the treatment of ruptured ectopic pregnancy.
5. Give your advice to a woman (three) months pregnant concerning her diet so that she will have ample mineral requirements for herself and fetus.
6. Discuss the management of frank breech presentation during the first stage, second stage. In what position is the patient always placed for breech delivery?
- 7-8. Give theories on the etiology of eclampsia, chief pathologic findings and method of treatment. What determines your advice to the patient concerning subsequent pregnancies?
9. Discuss the sphere of value of x-rays, radium and surgery in cancer of the cervix, fundus and ovary.
10. Describe briefly the phases through which the endometrium passes in one menstrual cycle.
11. How would you treat (1) cervical polyp (2) urethral caruncle?
12. Discuss the role of cauterization of the cervix in the prevention of cancer.

#### Transylvania University

THE JOURNAL, Nov. 30, 1940, page 1944, stated that Dr. Thomas H. Chivers graduated "from Transylvania University (now the University of Kentucky) in 1830," which statement, Dr. D. P. Hall of Louisville writes, is partially incorrect. Transylvania University is not now the University of Kentucky; the lineal descendant of the medical department of Transylvania University is now the School of Medicine of the University of Louisville. Transylvania University is located at Lexington, Ky.; at one time, for a few years, it assumed the title Kentucky University, but it was never the University of Kentucky (the present state institution).

#### New Sorority at Tennessee

The twenty-first chapter of Alpha Epsilon Iota, national women's medical sorority, was installed as the Omega Chapter at the University of Tennessee College of Medicine, Memphis, Sept. 28, 1940, with Dr. Mary Morris of St. Louis officiating. The new chapter had twelve charter members, all students except three who were alumni. Vera Lee Stewart was elected president of the sorority.

#### Louisiana's New Journal

Louisiana State University School of Medicine, New Orleans, has just published the first issue of the *Journal of the Louisiana State University School of Medicine*, which it is assumed is to replace the weekly newspaper known as the *Tiger*. Laurence B. Weiss '41 and Thomas R. Wilson '41 are co-editors of the new journal; Walter A. Salatch '42 is associate editor; Thomas M. Durham '43 is business manager. On the

editorial board are three members of the faculty in addition to the following students: Frank A. Cain '41 chairman; Burdette E. Trichel '41, Joe C. Much '42, George A. Degenshein '42 and Alvin F. St. Amant '43. The first issue contains scientific articles and interesting editorials and news items.

#### Virginia

The University of Virginia Department of Medicine, Charlottesville, recently announced the founding of a scholarship on bequest of the late Dr. James L. Minor, ophthalmologist, of Memphis, Tenn.

The first annual Phi Beta Pi Lecture at the University of Virginia Department of Medicine was given, October 14, by Dr. James B. Murphy of the Rockefeller Institute for Medical Research, New York, on "The Present Status of Cancer."

#### New Student Publication

*Tufts Medical Journal*, a new periodical published by the students of Tufts College Medical School, Boston, began publication in November. The first issue had 32 pages.

#### "DO YOU KNOW WHAT PHYSICIAN"

Following are answers to the questions appearing on page 349.

1. John Locke, who after a thorough preliminary education, entered Oxford, receiving his degree in medicine in 1666. He immediately entered medical practice. Later, in 1672, he was made secretary of the Board of Trade under Lord Shaftesbury, a position which he held with great distinction until 1675. Then he went to France, where at Montpellier and Paris he began work on his great contribution to philosophy, his *Essay Concerning Human Understanding*, which was published in 1690. In the same year he published "An Essay on Civil Government," which has been considered by some authorities as the most important contribution ever made to English constitutional law by an author who was not a lawyer by profession. Dr. Locke died in 1704.

2. William James, who was born in New York City in 1842 and graduated from Harvard Medical School in 1869. He was instructor and later assistant professor of anatomy and physiology at Harvard from 1872 to 1881, and in the latter year became professor of philosophy at Harvard, a position which he held until 1907. Among his writings were "The Will to Believe," "The Meaning of Truth," "Varieties of Religious Experience," "Essays in Radical Empiricism," "Some Principles of Philosophy" and "Pluralistic Universe." His philosophy was typically American. Dr. James died in 1910, the foremost philosopher and psychologist of his day.

3. Dr. George E. Goodfellow, who was born in Sierra County, Calif., Dec. 23, 1855. Dr. Goodfellow received his degree in medicine from the University of Wooster. He practiced medicine for a while, then entered the army as an acting assistant surgeon. He again returned to civil life and practiced medicine in Tombstone, Ariz., and again joined the army at the outbreak of the Spanish-American War, in which he served with distinction. After the battle of San Juan and El Caney, blindfolded and under a flag of truce, he was led into a Spanish camp, making several such trips, the final outcome of which was the surrender of the Spanish general. After the war Dr. Goodfellow returned to private practice in San Francisco, specializing in urology. Later he became chief surgeon of the Southern Pacific Railroad in Mexico and left San Francisco. He died in Los Angeles in 1910.



## Book Notices

**Hearing and Equilibrium.** By H. Macnaughton-Jones, M.B., B.Ch., B.A.O., Clinical Assistant, Ear and Throat Department, North London Hospital, London. Cloth. Price, \$2.50. Pp. 128, with 48 illustrations. Baltimore: William Wood & Company, 1940.

This treatise on the physics and the physiology of the ear is a welcome contribution to our literature. It is couched in terms which make comprehensible obtuse mathematical language to the otologist. It clarifies the working of natural laws in physics and explains phenomena difficult to visualize. It renews interest in how we hear and how we maintain balance or equilibrium.

The author's approach to the problems concerned is somewhat revolutionary and, as he expects, will be met with opposition. Time for study and consideration of the ideas the author advances will have to elapse before his views and presently held theories and principles are reconciled. The new concepts he advances too will engage serious study. At least here is presented a fresh outlook on problems with which otology is preoccupied.

The author sets out to prove that the configuration of the external auditory canal, the structure of the membrana tympani and the anatomy of the inner tympanic wall are so designed for the purpose of directing sound waves to the round window where they are received. The movements of the ossicular chain are given as a protective function. Their movements are clearly defined and illustrated. Their function of protection is designed to dampen excessive strain on the basilar membrane. This is accomplished through the muscles attached to the ossicles. Sound waves, transmitted to the fluids in the cochlea, produce a movement of the basilar membrane, which has a recoil force which lasts a specified time in each segment. This is understandable from the anatomic variations in the length of the basilar membrane in the cochlea as a whole. The author also presents intriguing explanations of the functions of the tectorial membrane and gives reason for the division of the scala tympani by Reissner's membrane, the function of the spiral septum and the mechanics of Corti's organ.

In themselves, the detailed studies and observations of the semicircular canals in their role for the maintenance of equilibrium are recommended to otologic students for serious consideration. They are worth while.

All portions of this monograph are freely illustrated with descriptive diagrams and other illustrations. These simplify both the physical and the engineering principles involved in the author's presentation of his conception of a moot physiologic problem.

In view of the renewed interest of the otologic surgeon toward seeking a surgical remedy for deafness, the ideas and conceptions presented in this volume furnish a new basis on which to evaluate the acoustic function. It may seem trite to say that the book must be read for appreciation of a new concept of the acoustic function, but the reviewer knows no other manner of emphasizing the importance he places on this little volume than to suggest that it be printed in its entirety in one of our current otologic publications. It should be in the hands of every student and practitioner of otology.

The reasoning is sound and logical. For the clinician, however, many aspects of the problem of how we hear and how we maintain our equilibrium are still unsettled.

**Starost: Trudy konferentsii po probleme geneza starosti i profilaktiki prezhdveremennogo starenia organizma.** Kiev, 17-19 Dekabrya 1938g. [Old Age: Reports of Conference on Problems of Genesis of Old Age and Prophylaxis of Premature Senescence of Organism.] Paper. Price, 22 rubles, 50 kopecks. Pp. 490, with illustrations. Kiev: Izdatelstvo Akademii Nauk USSR, 1939.

This large volume contains papers which were presented at the conference on old age which was held in Kiev in December 1938 under the auspices of the Ukrainian Academy of Sciences and the Institute of Experimental Biology. Old age is a serious economic problem in Soviet Russia in view of the liberal provisions of the old age pension act and the social security legislation. The volume contains some fifty papers dealing with various aspects of old age. There is a series of papers on the changes of the various tissues, organs and sys-

tems of the bodies due to old age with several excellent papers on changes in the central nervous system. The main value of the volume consists of the report of an exhaustive study of a group of 33 old persons between the ages of 90 and 142 years of age. The oldest people of Russia are found in Central Caucasus, and a separate expedition was sent there to study this group of the aged. Careful and painstaking studies were made of their metabolism and general physiology, with special stress on neuropsychiatric studies. In view of the tendency of the old people to exaggerate their age, careful attempts were made to check the age by matching it with certain historical events in the turbulent history of Caucasus. There was nothing unusual about the metabolism of these people which was different from any other group of old people. On the other hand, they all demonstrated an unusual stability of the nervous system with a history of extreme moderation and even frugality in all their habits from an early age, especially in the field of sexual activity. The volume abounds in many curious and interesting observations. In spite of the great mass of physiologic and metabolic studies, there is but little original in them. Throughout the volume there is a definite optimistic note in reference to old age, and the fact that we do not appreciate sufficiently the capacity of elderly persons in various occupations. A study of performance of older men in industry showed their extreme value for all sorts of skilled, technical occupations and especially in maintenance jobs which are vital in modern industrial plants. In connection with these studies, provisions were made in legislation to stop the granting of pensions at a certain fixed age. The old age is an elastic concept, and old age pensions should be granted only when persons are not able to work any more irrespective of the chronologic age. There is quite a good deal of feeling that old age as we see it at the present time is largely the result of some sort of intoxications and that the normal man in a normal environment should not get old until he is 150 years of age. The evenings of the meetings were devoted to general discussion with a stenographic account of the various opinions presented. There is an excellent bibliography of 855 references in which modern American authors are well represented.

**The 1940 Year Book of Public Health.** Edited by J. C. Geiger, M.D., Dr.P.H., Director of Public Health, City and County of San Francisco. Cloth. Price, \$3. Pp. 560. Chicago: Year Book Publishers, Inc., 1940.

Dr. J. C. Geiger, editor of this yearbook, has wisely selected abstracts from great numbers of publications and makes personal comment on almost every one of the abstracts of importance. The book covers every section of interest in modern public health. There is special emphasis on industrial hygiene, as well as discussions of borderline topics like health education, child hygiene and mental hygiene. The book is highly suggestive and the 296 editorial remarks are a fine commentary on modern ideas in public health.

**Clinical Electrocardiography.** By David Scherf, M.D., and Linn J. Boyd, M.D., F.A.C.P., Associate Clinical Professor of Medicine and Professor of Medicine, The New York Medical College, Flower and Fifth Avenue Hospitals, New York. Cloth. Price, \$6.25. Pp. 362, with 207 illustrations. St. Louis: C. V. Mosby Company, 1940.

This book of electrocardiography, according to the authors, is "not designed primarily for those beginning their study in this field." The text includes the usual material concerned with the normal electrocardiogram and various physiologic variations, the arrhythmias and disturbances of stimulus formation and conduction. The authors' discussions of the subjects of interference dissociation and parasystole and the bundle of Kent deserve especial commendation. The recent advances in the use of lead 4 are well analyzed and the point is made that "the value of chest leads is often exaggerated." Adversely, comment might be made regarding the reproduction of the details of the illustrative electrocardiograms. The authors also do not follow the terminology of that advocated by the American Heart Association. There is comparatively little discussion of the effect of drugs on the electrocardiogram. One might well disagree with the authors on the interpretation of the electrocardiogram with reference to endocrine disturbances. For example, "In some cases of ovarian insufficiency . . . distinct changes in the terminal deflection of the electrocardiogram are frequently found." The text has an extensive bibliography and is well indexed.

**Office Urology With a Section on Cystoscopy.** By P. S. Pelouze, M.D., Assistant Professor of Urology, University of Pennsylvania, Philadelphia. Cloth. Price, \$10. Pp. 766, with 443 illustrations. Philadelphia & London: W. B. Saunders Company, 1940.

In giving his reason for the presentation of this book, the author states that he has attempted to comply with the request of the publisher to write a book on his experience in office urologic diagnosis and treatment. "One cannot spend years at office urology without feeling that there are many operations performed that rather easily might have been avoided by early attention to little things. It is of these little things that I have tried to write. . . ." Again, "there is little need that a book of this type be made a repository for medical curiosities. If there is a need, it is for the portrayal of the things that doctors see and treat in their daily experiences, and it is to these that the book is devoted." When the author sticks to his concept of the mandate, he makes his book exceptionally lucid, informative and authoritative. When the book goes beyond the self-imposed *raison d'être* and includes major surgical urology and rare urologic conditions that are obviously not in the category of office urology, it flattens somewhat. The arrangement of the subject matter begins logically with office setup and covers urologic anatomy, physiology, history taking, examinations, diagnoses, symptoms, treatment and diseases of the urogenital system. It contains a well written discussion of the sexual problems and an exceptionally good chapter on cystoscopy, its technic and interpretation of observations. One has the feeling that, if books on the other specialties were as well conceived and handled, a careful perusal of them would perforce enhance the efficiency of the physician in his general practice.

**Operative Surgery.** By J. Shelton Horsley, M.D., LL.D., F.A.C.S., Attending Surgeon, St. Elizabeth's Hospital, Richmond, Va., and Isaac A. Bigler, M.D., Professor of Surgery, Medical College of Virginia, Richmond. With Contributions by C. C. Coleman, M.D., F.A.C.S., Professor of Neurological Surgery, Medical College of Virginia, Austin I. Dodson, M.D., F.A.C.S., Professor of Urology, Medical College of Virginia, John S. Horsley, Jr., M.D., Associate Professor of Surgery, Medical College of Virginia, and Donald M. Faulkner, M.D., Associate Professor of Orthopedic Surgery, Medical College of Virginia. Volumes I and II. Fifth edition. Cloth. Price, \$18 per set. Pp. 768; 769-1567, with 1,391 illustrations by Helen Lorraine. St. Louis: C. V. Mosby Company, 1940.

These two volumes represent an interesting development of modern surgery. Those who have the opportunity should read the prefaces of all five editions, which are presented at the beginning of volume I. At first almost entirely the work of the senior author, the work, because of the rapid growth of modern surgery, forced not only new editions but also the addition of several collaborators. At present it is difficult to evaluate the importance of such contributions to surgical literature. They do respond to a definite demand, and in spite of increasing specialization of surgeons the general surgeon, like the general practitioner, is likely to be with us for some time. The material is not encyclopedic in character, but a number of operations for various disorders are usually presented. The technic of the operations is couched in clear language and a number of good illustrations fortify the text. One of the more pleasing points is the frequent indication by the author of the method he prefers and why he prefers it. The first volume is devoted to general principles and surgery of the head, neck and thoracic regions, as well as orthopedic and plastic surgery. The second includes the remainder of the alimentary tract, the abdominal wall and neurosurgery. The urogenital system also is discussed in this volume. The comprehensive scope of the work, its compact nature and its avoidance of encumbering and obsolete operative technics enhance the value of this work to general practitioners and surgeons alike.

**Diseases of Workers.** The Latin Text of *De Morbis Artificum* [by] Bernardino Ramazzini, 1713, revised, with translations and notes by Wilmer Cave Wright. The History of Medicine Series issued under the auspices of the Library of the New York Academy of Medicine, Number 7. Cloth. Price, \$5. Pp. 549, with 3 illustrations. Chicago: University of Chicago Press, 1940.

Bernardino Ramazzini (1633-1714), professor of the theory of medicine at Modena and of practical medicine at Padua, is distinguished as the author of the first important treatise on occupational diseases. Readers of this excellent translation will find his work comprehensive, solicitous for the welfare even of

cleaners of privies and cesspits, keen in the search for the physical causes of the afflictions of workmen, and alert to suggest methods of prevention. He evidently was a good observer and an excellent judge of human kind; witness the pungent remark concerning farmers: "It follows that in my opinion men of this class should be treated by the direct and summary method; any other that is roundabout and calls for an outfit of various sorts gradually consumes the strength of these peasant folk: 'Who seeks to cure but makes it worse.'" Mrs. Wright, who translated the *De contagione* of Fracastorius, is professor emeritus of Greek in Bryn Mawr. She brings to this task a familiarity with the classics and Italian medicine of the seventeenth century. Her introduction reviews the life of this great scholar, and her critical bibliography and extensive notes illumine the translation and enlarge the picture of medical practice in the days of Fracastorius and Ramazzini. Readers of her well wrought translation will enjoy not only this rather intimate picture of medical practice of the seventeenth century in Italian university cities but also the revelation of the then current medical controversies and the vivid and humorous picture of the social, business and industrial life in Italy from 1680 to 1713.

**Actas de la décima Conferencia sanitaria panamericana, Bogotá, septiembre 4-14, 1938. Oficina sanitaria panamericana, publicación No. 136. Cloth. Pp. 941, with illustrations. Washington, D. C.: Pan American Sanitary Bureau, 1939.**

This volume contains the general acts of the tenth Pan American Conference, held in Bogotá Sept. 4-14, 1938, and the articles on official topics on matters of public health and sanitation, with reports on the progress from the date of the ninth Pan American Sanitary Conference, which was held in Buenos Aires in 1938, up to now. The articles presented in the course of the sixteen different plenary sessions are concerned with epidemiology and prevention of yellow fever, pestilential diseases, infectious diseases transmitted by a virus and leprosy, international relations for sanitation in aviation and navigation, control of stupefactive drugs, venereal diseases, parasitic diseases, potability of water, rural sanitation, food, hygiene for mothers and infants, and eugenics. The articles of the extraordinary sessions are concerned with the history of malarial sanitation, especially related to the discovery of quinine, and memorial honors for workers in hygiene. The articles of the closing session are reports of executive work, motions and resolutions. The book ends with an appendix with reports of delegates and directors of public health of Pan American countries on the fulfillment of the resolutions adopted in the nine Pan American sanitary conferences. The book is presented to sanitary, hygienic and medical libraries with the compliments of the Pan American Sanitary Bureau of Washington, D. C.

**Essentials of the Diagnostic Examination.** By John B. Youmans, B.A., M.S., M.D., Associate Professor of Medicine and Director of Postgraduate Instruction, Vanderbilt University Medical School, Nashville. Fabrikoid. Price, \$3. Pp. 417, with 36 illustrations. New York: Commonwealth Fund; London: Oxford University Press, 1940.

This is a dapper little volume, well printed on thin paper and of such size, shape and weight as to fit conveniently into one's pocket or bag. It is unpretentious. The essentials of the diagnostic examination are described, history taking in sixteen pages, physical examination in 142 pages and laboratory tests in the remaining 218 pages. On first sight this spacing of the material may appear unusual and as if undue emphasis was placed on the laboratory and too little on history taking. Such is not the case. One cannot tell how to take a good history beyond suggesting bare outlines. The technic of physical examination is easier to describe and certainly the author outlines the methods of physical examination in a satisfactory manner, including a common sense, easily understandable description of neurologic examination. The laboratory manual part of the book must have been the least interesting to write. It describes ordinary clinical laboratory work and methods with clarity and detail. On the whole, the new *Diagnostic Examination* is a good 1940 model. Every doctor ought to have an up-to-date booklet of this character as part of his standard equipment, in constant use and as well thumbed as any priest's book of prayers. This particular *Diagnostic Examination* contains few errors, is handy and, above all, is put together by a competent clinician thoroughly familiar with all of which he writes. It deserves a successful life.

## Queries and Minor Notes

THE ANSWERS HERE PUBLISHED HAVE BEEN PREPARED BY COMPETENT AUTHORITIES. THEY DO NOT, HOWEVER, REPRESENT THE OPINIONS OF ANY OFFICIAL BODIES UNLESS SPECIFICALLY STATED IN THE REPLY. ANONYMOUS COMMUNICATIONS AND QUERIES ON POSTAL CARDS WILL NOT BE NOTICED. EVERY LETTER MUST CONTAIN THE WRITER'S NAME AND ADDRESS, BUT THESE WILL BE OMITTED ON REQUEST.

### SULFANILAMIDE DERIVATIVES AND QUINIDINE FOR CYSTITIS AND CARDIAC FIBRILLATION

*To the Editor:*—A patient with a severe chronic cystitis also has a cardiac fibrillation which was brought on by a toxic goiter. The goiter was removed several years ago but the cardiac fibrillation can be controlled only by quinidine treatment. The bladder symptoms improve temporarily by irrigating with boric acid solution and instillation of mild protein silver. Methenamine does not seem to help her much. The urologist after cystoscopic examination confirmed the diagnosis of chronic cystitis due to colon bacilli with laboratory evidence of a slight degree of infection in the right kidney pelvis. Would it be safe to give her some one of the sulfanilamide group, such as sulfathiazole, at the same time as she is taking the quinidine sulfate (8 grains, or 0.5 Gm., a day) and phenobarbital?

M.D., Illinois.

*ANSWER:*—Sulfanilamide or its derivatives such as sulfapyridine or sulfathiazole should be administered with care to patients who are suffering from cardiac dysfunction. This is especially true if heart failure is present. It is probable that some form of mandelic acid should be tried before sulfonamide derivatives are used in this particular case. If this therapy did not bring about the desired results, one could use sulfathiazole, giving about 1 Gm. three times a day at 8 a. m., 2 p. m. and 8 p. m. Care should be taken that the urine output is maintained at least 1,000 cc. a day, and it also would be wise to determine whether or not impaired renal function is present. This can easily be accomplished by doing a phenol-sulfonphthalein test. If this test shows impairment of renal function care must be taken, if sulfathiazole is prescribed, to prevent the drug from accumulating in the blood and tissues of the patient because, with decreased kidney function, sulfonamide drugs are not excreted in a normal fashion. As far as is known at the present time, the administration of quinidine sulfate and phenobarbital does not constitute contraindications for sulfonamide therapy.

### SOLDERING FLUID CONTAINING HYDROCHLORIC ACID, AND PULMONARY FIBROSIS

*To the Editor:*—A patient who has been a tinsmith for about twenty years and has used muriatic acid freely in his work now has quite severe dyspnea and yet not many definite physical abnormalities to account for it except what seems to be a generalized fibrosis of the lungs as seen on the x-ray plate. Is it possible that the long continued use of this acid will cause such a change when no attempt is made to draw the fumes away from the workers? If so, will Spear soldering fluid, grade super, made by the Jordan Company, Chicago, do the same? He is going to the United States for care in the hope that he has a curable condition but we want to prevent the occurrence of a similar condition in his sons, who are doing the same work. They say this Spear fluid does not give off many fumes and is not so choking in its effect when breathed. If these fumes will cause a fibrosis, what can be done for patients when they reach this stage of disabling dyspnea? Is diathermy of any value?

David Hoehn, M.D., Fairbanks, Alaska.

*ANSWER:*—The characteristic action of hydrochloric acid vapors leads to erosion of the teeth, extensive caries or the loss of teeth, together with acute episodes of conjunctivitis, pharyngitis, bronchitis with occasional pneumonia or minor pulmonary hemorrhage. Unless some or all of these manifestations now exist or have existed in the past, the present disabling dyspnea and fibrosis probably is not associated with hydrochloric acid as the cause. Koelsch (Ueber die Gesundheitsverhältnisse der Arbeiter in der Saureindustrie: Referat erstattet für ein Gutachten des Reichsgesundheitsrats) cites the German records indicating that this class of workers are infrequently affected with tuberculosis but other respiratory diseases are more frequent than for other classes of chemical workers. Death rates among tinsmiths from all causes barely exceed the general average, and the causes of death do not include any characteristic occupational diseases.

It is not known that these hydrochloric acid vapors or the vapors from any other soldering fluid may occasion any pulmonary fibrosis distinctive of any special occupational disease. From long years of exposure to any respiratory irritant, chronic sinus involvement may be expected which will eventuate in

heavier markings found in x-ray films of the lungs. It is reasonable to believe that twenty years of exposure to hydrochloric acid vapors might increase the amount of pulmonary fibrosis, but conversely there is no warrant to associate this noncharacteristic increased fibrosis with total disability, marked dyspnea or any other feature pointing to the hydrochloric acid as the direct and specific cause. If it may be assumed that the present dyspnea and disability are associated with the fibrosis, it is not known that any diminution of the fibrosis itself can be brought about through any treatment, including diathermy. On the other hand, thorough examination may reveal causes of the dyspnea unrelated to the fibrosis which may prove to be amenable to treatment.

Spear soldering fluid, manufactured by the Jordan Company, of Chicago, consists of zinc cut in hydrochloric acid, thus leading to zinc chloride. The manufacturer states that proper manipulation eventuates in a soldering fluid basic in nature and thus without any content of free hydrochloric acid. This manufacturer points out that impure zinc, if used, might lead to the presence of unwanted harmful metals, such as lead and arsenic. The claim is made that such impurities are eliminated in the Spear fluid. It is believed that this particular soldering fluid, like others, even though free from hydrochloric acid, still may constitute a skin irritant and its vapors an irritant to the conjunctivas and respiratory tract.

### PROBABLE TUBERCULOUS ARTHRITIS

*To the Editor:*—A white woman aged 37, married, has had a firm swelling and somewhat stiffened left knee for one year. The condition began insidiously and has been treated as arthritis with no change. There is some fixation, and pain is precipitated by wide excursions. X-ray examination shows widening of the joint space on one side with haziness of part of the joint surface of the femur. Complete rest of the knee joint was brought about by a plaster cast to the leg for one month. The condition remains the same except that there is more fixation and more pain when walking and especially when climbing stairs. A physical examination at this time reveals no demonstrable pathologic condition. In the family history an older sister died of pulmonary tuberculosis. In childhood they were close and three years after the older sister left home she died of pulmonary tuberculosis (now fourteen years ago). The personal history brings out that the patient has enjoyed usual good health. She has been married for eight years. The first pregnancy terminated spontaneously at three months. The second pregnancy was a full term stillbirth and the third pregnancy resulted in a full term normal infant now 2½ years old. About three years ago in the winter she had a bad attack of "flu" (in her own words) from which she did not really recover. She then had many moist rales over the apex, which persisted after cough with a temperature of 99.6 F., respirations 20 and pulse 104. I made a diagnosis of pulmonary tuberculosis. The next day the chest was roentgenographed and the report is that there is no evidence of tuberculosis but extensive bronchitis. Under treatment the cough gradually subsided and the patient gained weight. She later went through a normal and uneventful pregnancy and now has a child 2½ years old. She enjoyed apparent good health until one year ago, when the knee began to swell and hurt. The knee now remains apparently the same size as at onset. The joint has been at rest four weeks and the leg is back in the cast for an additional four weeks. Will a diseased joint like this come back to useful function if fixed too long? A synovectomy is proposed if fixation fails. After the synovial membrane is removed, where will the joint fluid come from so that the joint will function normally? There is some fluid in the joint that could be used in a guinea pig. Is the guinea pig test reliable and accepted now as an indisputable fact of diagnosis of tuberculosis? I have heard that some pathologists put little stock in the test for they say that guinea pigs frequently die of tuberculosis even without being inoculated with tuberculous material. Incidentally, shortly after the chest x-ray films were made a purified protein derivative second strength test was made on her and the reading is recorded as definitely positive.

M.D., Ohio.

*ANSWER:*—The history of a monarticular progressive arthritis which has failed to yield to conservative treatment is suggestive of tuberculosis of the joint. The haziness of the joint space and of the bones as shown in the x-ray film and also the family history and past history of the patient lend further evidence in favor of this diagnosis. The patient should have the knee joint aspirated and the fluid injected into a guinea pig. Guinea pig inoculation is a reliable test for tuberculosis when it is positive. A negative test does not necessarily mean that the patient does not have tuberculosis. It is advisable that two guinea pigs be injected in case one should die before sufficient time has elapsed for the disease to become manifest. If the guinea pig test is positive, arthrodesis of the joint might be advisable, as it is doubtful that recovery from tuberculosis will occur in an adult as long as there is movement in the joint. If the guinea pig test is negative and the patient continues to be disabled and the joint does not yield to conservative treatment, a biopsy and probably an arthrodesis are indicated even if definite tuberculosis cannot be proved, as this seems to be a progressive destructive lesion.

## ABDOMINAL PAIN AND VASCULAR FAILURE

**To the Editor:**—A young woman complained of a vague abdominal pain associated with nausea, subnormal temperature, pulse and respiratory rate, low blood pressure and excessive weakness. There was only slight tenderness in the right lower quadrant with almost no rigidity. The past history was negative. On admission to the local hospital a blood study revealed a total white count of 22,800 with a differential count of 93 per cent polymorphonuclears and 7 per cent lymphocytes. No abnormal cells were seen. The red blood count and hemoglobin were apparently normal. The white cell count was repeated six hours later and it was seen to have dropped to 16,200. The following morning the count was 14,600 and prior to discharge the next day it was 12,700 with 64 per cent polymorphonuclears, 32 per cent lymphocytes and 4 per cent eosinophils. While at the hospital the patient rallied almost immediately with intravenous saline solution and stimulative therapy; the abdominal pain disappeared spontaneously, as did the tenderness. Because of recurrent furuncles I have been giving the patient a course of *Staphylococcus aureus* vaccine, using graduated doses, every three days. The last dose, which was 10 minims (0.6 cc.), was given two days prior to the onset of the present complaint. At no time, however, has there been any evidence of hypersensitiveness to the vaccine. 1. Could a minute perforation in the appendix being sealed off immediately by the omentum be a possible cause of such a clinical picture? 2. Could the vaccine contribute to the elevated white cell count in the face of such a toxic shock? 3. Is there any chance of the picture being allergic in nature, because of the eosinophils which had not appeared in the three earlier counts?

Sigmund J. Posner, M.D., Ludlow, Mass.

**ANSWER.**—It is difficult, if not impossible, to explain accurately what happened in this case. The symptoms of subnormal temperature, pulse and respiratory rate together with low blood pressure and excessive weakness resemble those seen in peripheral circulatory failure. The rapid response of the patient to stimulative treatment and the intravenous infusion of physiologic solution of sodium chloride is quite consistent with such a picture. Peripheral circulatory failure may be caused by the rupture of an acutely inflamed appendix. The initial leukocyte count is quite in keeping with an acute appendicitis and yet it is most unusual, but not impossible, for an acutely inflamed appendix to rupture with only "vague abdominal pain." Just preceding and at the time of the rupture one expects rather sharp pain, which is relieved by the rupture.

A simple acute gastro-enteritis could be responsible for the symptoms, including the blood count, described.

An allergic response is capable of producing peripheral vascular failure but there are many objections to a diagnosis of anaphylactic shock in this case. Anaphylactic shock seldom waits two days to make its appearance. Except in foreign protein shock, which this was not, the leukocyte count does not rise above 20,000. Four per cent of eosinophils with a total white count of 12,700 cannot be called a true eosinophilia. The eosinophils must rise above 600 per cubic millimeter before such a diagnosis can be made. In this case there were 508. It seems unlikely that the vaccine was involved in any way.

The absence of eosinophils in the really high white counts is not unusual. The eosinophils frequently disappear from the circulating blood with a sudden upsurge of the neutrophils. Reappearance of the eosinophils is considered an omen that the cause of the neutrophilia is subsiding.

## YEASTS IN URINE AND PROSTATE

**To the Editor:**—A woman of about 55 has been complaining of some urinary disturbance for the past year. Catheterized specimens and stained smears of the sediment with Gram stain reveal in every instance mycelia and large quantities of pus. I have tried various forms of treatment, including irrigations, and sulfanilamide, with no measure of success. A man aged 30 had a gonorrheal infection about two years ago and now has a large boggy prostate. Cultures taken from the prostatic secretion after massage show yeast cells in large numbers. I would appreciate any suggestions as to the treatment in these two cases.

B. B. Coker, M.D., Durant, Okla.

**ANSWER.**—Yeasts are rarely found in the vesical urine. Their occurrence in the prostatic secretion is even more rare. They are usually considered as saprophytes, and whether or not they occur as true pathogens in the prostate and bladder is open to question.

Bladder instillations of 30 cc. (1 ounce) of gentian violet, 1:1,500 solution, two or three times weekly are often effective in eliminating yeast from the urine. Any associated bacterial infection should be treated with the chemotherapeutic agents most effective for that particular organism, including the sulfanilamide compounds and mandelic acid. In the woman the search for yeast infection in the vagina should be made and, if present, treatment should be instituted. Daily application of 1 to 2 per cent gentian violet is sometimes effective. In the man, when yeasts are found in the prostate deep urethral instillations of 1:1,500 gentian violet solution plus prostatic massage should be beneficial. Diabetes mellitus, if present, should be strictly controlled.

## KERATOCONUS AND PREGNANCY

**To the Editor:**—Will you please give me some information on the present status of the relationship of pregnancy to keratoconus. I am particularly interested to know whether or not pregnancy will aggravate the condition.

M.D., California.

**ANSWER.**—There are no specific cases reported in the literature of an increase in a keratoconus due to pregnancy. But there is a widespread opinion among those familiar with the condition that an endocrine disturbance plays a great part in the causation and progress. For instance, Duke-Elder (Textbook of Ophthalmology, vol. 2, p. 2028) said "It is generally admitted that the ductless glands exercise a very potent influence over growth processes and it would not be surprising that an upset of their balance should alter the condition of a tissue which is primarily supportive, a view borne out by its usual incidence about the time of puberty and its preference for females." Two pages later he said "The endocrine system should be minutely overhauled and any imbalance looked into, especial attention being paid to early menstrual disturbances in girls; thyroid and female sex hormones may be indicated." With these factors in mind, it would not be surprising if pregnancy would exert a more or less deleterious influence on keratoconus. But there is no specific evidence to support that statement.

## TREATMENT OF TRICHOCEPHALUS TRICHIURIS

**To the Editor:**—Please outline treatment for *Trichocephalus trichiuris* infection in a 9 months old infant. Repeated treatments with hexylresorcinol in 1½ grain doses given over a period of two months and at two week intervals have been ineffective.

Beulah M. Kittrell, M.D., Maryville, Tenn.

**ANSWER.**—The treatment of *Trichocephalus trichiuris* infection is at the present time unsatisfactory. Hexylresorcinol has been found about as effective as any other drug in this condition, but it has been impossible to clear up any high percentage of cases even with this drug. The only thing that is known in which real success has been reported is the treatment with the sap of the fig tree. The active principle of this sap has been shown to be a proteolytic enzyme which digests the worm. Although the natives have used this for generations in the treatment of worms, this substance cannot be recommended for treatment in human beings at present, as it is known that it can digest the intestinal tract if the mucosa is sufficiently irritated. It has no effect whatever on the normal intestinal tract.

## OINTMENT BASE FOR SULFANILAMIDE

**To the Editor:**—I found that powdered sulfanilamide healed two infected scalp wounds rapidly. However the powder, serum, blood and pus formed a crust. When this was removed it tore away some of the epithelium. What would be a good base for a sulfanilamide ointment?

E. P. S. Miller, M.D., Chicago.

**ANSWER.**—The following formula makes a satisfactory sulfanilamide ointment:

1. Dissolve 10 parts of sulfanilamide in 25 parts of hot water (almost boiling). Filter.
2. To 4 parts of sodium alginate add 75 parts of boiling water, emulsify and then strain the resulting mucilaginous mixture through fine gauze. Mix the filtered sulfanilamide solution and the sodium alginate while hot, and stir this mixture until cool.
3. Add 16 parts of anhydrous wool fat, 1 part of sodium chloride dissolved in 4 parts of water, and 78 parts of white petrolatum base to the sulfanilamide-sodium alginate mixture and mix until smooth.

This ointment can be used not only on surface wounds but also on mucous membrane surfaces such as the conjunctivas.

## SULFANILAMIDE ADMINISTRATION TO NURSING MOTHER

**To the Editor:**—What harmful effect if any on a nursing baby 3 weeks old would sulfanilamide have if given to the mother in full doses in a case of puerperal infection?

Thomas E. Brewer, M.D., Quitman, Ark.

**ANSWER.**—Experience has shown that the amount of sulfanilamide or one of its derivatives which a nursing child might receive from its mother, if she is taking full doses of sulfanilamide or one of its derivatives, would be negligible. So far there have been no reports in medical literature of untoward effects arising in a nursing baby whose mother was receiving sulfanilamide.

# The Journal of the American Medical Association

Published Under the Auspices of the Board of Trustees

VOL. 116, No. 5

COPYRIGHT, 1941, BY AMERICAN MEDICAL ASSOCIATION  
CHICAGO, ILLINOIS

FEBRUARY 1, 1941

## COMBINED ARTIFICIAL FEVER- CHEMOTHERAPY

IN GONOCOCCIC INFECTIONS RESISTANT TO  
CHEMOTHERAPY

H. WORLEY KENDELL, M.D.

DONALD L. ROSE, M.D.

AND

WALTER M. SIMPSON, M.D.

DAYTON, OHIO

The widespread acceptance of sulfanilamide and other sulfanil compounds as effective agents in the treatment of gonococcal infections has modified the value of all preexisting types of therapy. The rapidity with which many cases yield to intelligent and controlled administration of these drugs has obviated the necessity for the use of accessory therapeutic agents in such cases. The brilliance of such results has been dimmed somewhat by the development of several circumstances which will prevent the ultimate eradication of the disease: the asymptomatic carrier,<sup>1</sup> the development of chemotherapy-fast strains of the gonococcus<sup>2</sup> and the occurrence of relapse after apparent cure.<sup>3</sup> Even in instances in which the patient has received what was thought to be adequate treatment, sulfanilamide may fail completely to eradicate the infection. Indeed, in a survey by Dees and Young<sup>4</sup> of 2,727 well analyzed cases collected from the literature only 1,848 (68 per cent) could be classified as immediate cures and an additional 4 per cent as delayed cures. This observation does not imply that sulfanilamide is of limited value in the treatment of gonorrhea; rather, it indicates that even with ideal treatment conditions there will be a considerable proportion of such patients who are not cured by chemicals available at the present time.

Many investigators<sup>5</sup> have demonstrated the value of artificial fever in the treatment of gonorrhea during

the presulfanilamide era. Relatively few publications have appeared concerning the effectiveness of artificial fever therapy since the introduction of modern chemotherapy.<sup>6</sup> A few recent publications have dealt with the action of artificial fever in cases of gonorrhea refractory to chemotherapy.<sup>7</sup>

It is our purpose in this paper to point out the value of artificial fever therapy, either alone or combined with chemotherapy, in a series of patients with gonorrhea known to be resistant to sulfanilamide or sulfapyridine.

### EVOLUTION OF FEVER DOSAGE

Treatment of gonococcal infections with artificial fever began in the Kettering Institute for Medical Research in 1932.<sup>8</sup> The first patient so treated was referred for fever therapy because of refractory latent syphilis; he also manifested concurrent clinical and bacteriologic evidence of active gonococcal urethritis and arthritis. During the course of treatment for syphilis, which consisted of five hour sessions at 105-106 F. given once weekly, the arthritis improved immediately and the signs of urethritis gradually disappeared. Succeeding patients treated primarily for gonococcal arthritis received the same fever dosage.<sup>9</sup>

With the observation of Anderson, Arnold, Trautman and Faget<sup>10</sup> in 1934 that semiweekly treatments hastened the disappearance of the urethritis, interest shifted from the treatment of gonococcal arthritis per se to include the eradication of the coexistent genital infec-

5 (continued).

Desjardins, A. U.; Stuhler, L. G., and Popp, W. C.: Fever Therapy for Gonococcal Infections, *J. A. M. A.* **106**:690 (Feb. 29) 1936.

Owens, C. A.: The Value of Fever Therapy for Gonorrhea, *ibid.* **107**:1942 (Dec. 12) 1936.

Humiston, H. W.: Heat and Fever in Treatment of Gonococcus Infections, *Am. J. Syph., Gonorr. & Ven. Dis.* **21**:554 (Sept.) 1937.

Warren, S. L.; Scott, W. W., and Carpenter, C. M.: Artificially Induced Fever for the Treatment of Gonococcal Infections in the Male, *J. A. M. A.* **109**:1430 (Oct. 30) 1937.

Desjardins, A. U.; Popp, W. C., and Stuhler, L. G.: Fever Therapy for Gonococcal Infections, *M. Clin. North America* **21**:885 (May) 1937.

Parsons, E. H.; Bowman, P. N., and Plummer, D. E.: Artificial Fever Therapy of Gonorrhea in the Male, *J. A. M. A.* **109**:18 (July 3) 1937.

Schnabel, T. C., and Fetter, F.: Fever Therapy in Gonococcal Infections, with Especial Reference to Gonococcal Arthritis, *Am. J. Syph., Gonorr. & Ven. Dis.* **22**:39 (Jan.) 1938.

Kendell, Webb and Simpson.<sup>9</sup>

6. Krusen, F. H.: Summary of Results of Fever Therapy for Gonorrhea with Follow-up Reports, *Proc. Staff Meet., Mayo Clin.* **13**:297 (May 11) 1938.

Ballenger, E. G.; Elder, O. F.; McDonald, H. P., and Coleman, R. C., Jr.: Sulfanilamide: I. General Discussion of the Drug; II. Sulfanilamide with the Sealing Treatment of Gonorrhea; III. Sulfanilamide in Combination with Artificial Fever, *South. Surgeon* **7**:204 (June) 1938; Sulfanilamide and Thermotherapy, *J. A. M. A.* **109**:1037 (Sept. 25) 1937; Artificial Fever in Combination with Sulfanilamide, *Urol. & Cutan. Rev.* **43**:441 (July) 1939. Belt and Folkenberg.<sup>21</sup>

7. Elkins and Krusen.<sup>22</sup> Owens, Wright and Lewis.<sup>23</sup>

8. Simpson, W. M.: Artificial Fever Therapy of Syphilis and Gonococcal Infections, *Brit. J. Ven. Dis.* **12**:133 (July) 1936. Kendell, Webb and Simpson.<sup>9</sup>

9. Kendell, H. W.; Webb, W. W., and Simpson, W. M.: Artificial Fever Therapy of Gonorrheal Arthritis, *Am. J. Surg.* **24**:428 (Sept.) 1935.

10. Anderson, T. B. H.; Arnold, R. C.; Trautman, J. A., and Faget, G. H., in Abstracts of Papers and Discussions, Fifth Annual Fever Conference, Dayton, Ohio, 1935, p. 33.

From the Kettering Institute for Medical Research, Miami Valley Hospital.

1. Pelouze, P. S.: Gonorrhea in the Male and Female, Philadelphia, W. B. Saunders Company, 1939, pp. 159-169.

2. Westphal, L.; Charles, R. L., and Carpenter, C. M.: The Development of Sulfapyridine-Fast Strains of the Gonococcus, *J. Bact.* **39**:47 (Jan.) 1940.

3. Boak, Ruth A.; Charles, R. L., and Carpenter, C. M.: Tolerance of the Gonococcus in Vitro for Increasing Concentrations of Sulfanilamide, *Tr. Am. Neisserian M. Soc.*, 1939, p. 118.

4. Herrold, R. D., and Palmer, E.: The Influence of Sulfanilamide on Gonococci and Gonococcal Infections, *Am. J. Syph., Gonorr. & Ven. Dis.* **22**:705 (Nov.) 1938.

5. Cokkinis, A. J., and McElligott, G. L. M.: Relapses After Sulfonamide Cure of Gonorrhea, *Brit. M. J.* **2**:1080 (Dec. 2) 1939.

6. Cokkinis, A. J.: Discussion of Sulfonamide Therapy in Gonorrhea, *Brit. J. Ven. Dis.* **15**:117 (April) 1939.

7. Dees, J. E., and Young, H. H.: Present Status of Sulfanilamide Therapy in Gonorrhea, *Ven. Dis. Inform.* **20**:33 (Feb.) 1939.

8. These include:

9. Bierman, W., and Levenson, C.: The Treatment of Gonorrheal Arthritis by Means of Systemic and Additional Focal Heating, *Am. J. M. Sc.* **191**:55 (Jan.) 1936.

(Continued in next column)

tion. Attention thus became concentrated on shortening the treatment interval in order to hasten recovery. This plan was quickly adopted by other workers. Desjardins<sup>11</sup> in 1935 reported on the fever treatment of 56 patients giving various manifestations of gonococcic infection with semiweekly five hour sessions at 105-106 F.; after an average of five such sessions, cure was effected. Other workers<sup>5</sup> reported essentially similar results.

Not until the important researches of Carpenter, Boak, Mucci and Warren<sup>12</sup> on the thermolability of different strains of gonococci were the foundations laid for the accurate dosage of fever in the treatment of this infection. Unfortunately, the determination of the thermal death time for a given strain of gonococcus and the subsequent regulation of fever dosage according to the thermal death time of each strain had many barriers in the way of its practical application. Such a procedure is not adaptable to routine performance in the average fever therapy clinic.

Summary of Results

Type of Treatment	Number of Cases	Cure Following Single Session	Average No. of Treatments to Effect	Duration of Disease			
				Under 3 Mos.		Over 3 Mos.	
				Male	Female	Male	Female
8 hrs. 106.6 F. fever	9	9.9%	2.4	3	2	3	1
10 hrs. 106.6 F. fever	11	63.6%	1.45	4	1	6	..
10 hrs. 106.6 F. fever and 10 days intensive sulfanilamide..	5	60.0%	1.8	4	..	1	..
10 hrs. 106.6 F. fever and oral sulfanilamide during 18 hrs. before fever.....	20	100.0%	1.0	7	1	10	1
10 hrs. 106.6 F. fever and intravenous sulfanilamide immediately before fever treatment.....	16	81.9%	1.2	4	3	5	4
10 hrs. 106.6 F. fever and Promin during fever treatment.....	11	63.6%	1.3	4	2	5	..
10 hrs. 106.6 F. fever and Promin during 18 hrs. before fever	11	100.0%	1.0	4	2	3	2
Total.....	83	.....	...	30	11	33	8

Nevertheless, these researches provided the impetus toward the administration of fever in longer sessions, even if the dosage of fever at one session did not approximate the thermal death time of the organism.

At that time the inadequate apparatus and the fragmentary knowledge of the physiology of fever did not permit the use of sustained fever at high levels for long periods. Although long sessions of fever at 106-107 F. were given in this earlier period, they were usually looked on as technical feats and were certainly not to be recommended for the routine treatment of gonorrhea. For this reason the practice of giving multiple short treatments at 105-106 F. was retained.

With improvements in design of the air conditioned cabinet, better insulation, the use of thermostat controls and electrical indicating or recording rectal thermometers, it was found that longer sessions of fever could be tolerated without difficulty, if administered by skilled workers. These factors, combined with a recognition of the necessity for compensating for sodium chloride

and fluid loss, cognizance of the dangers inherent in certain types of sedatives and the ability to detect warning signals early, have measurably increased both the safety and the comfort requisites for the satisfactory and practicable administration of artificial fever.

Since it had been observed that longer sessions of fever reduced the total number of treatments required, Krusen<sup>13</sup> in 1937 began using ten hour sessions at 106-107 F. instead of the then standard five hour to eight hour treatments at 105-106 F. By this means he was able to reduce the number of treatments from an average of five to one and one tenth.

At the present time the technic of administering artificial fever has progressed to the point at which patients may now receive a ten hour session at 106.6 F. with far more safety and comfort than was possible with shorter sessions at lower temperature levels in former years. In skilled hands, treatments of this type may be prescribed with a frequency which approaches routine.

SELECTION OF PATIENTS FOR FEVER TREATMENT

(a) *Previous Chemotherapy.*—An earnest attempt has been made to have all the patients included in this report completely comparable in one respect, namely resistance to chemotherapy. Earlier patients had received only sulfanilamide, since sulfapyridine was not at that time generally available. Those subsequently treated had received either sulfanilamide or sulfapyridine or both. A few had received relatively small amounts of chemotherapy because of the development of one or more of the following untoward reactions: blurred vision, extreme nausea and vomiting, acute hemolytic anemia, fever, hepatitis, jaundice and dermatitis.

(b) *Duration of the Disease.*—Fever therapy has not been limited to any particular manifestation or stage of the disease. Since we dealt with drug-resistant patients, no one treated had had the disease for less than two weeks. No attempt has been made to classify the condition as acute, subacute or chronic on the basis of duration of symptoms. The patients are arbitrarily divided into two groups: those in whom the duration of the disease was more than three months or less than three months. The table reveals that approximately one half of the patients fall into each group.

(c) *Complications of the Disease.*—No patient was treated for uncomplicated anterior urethritis. All varieties of complications were treated, varying from the relatively minor one of prostatitis to severe panpelvic inflammation. Seven patients were completely asymptomatic, falling into the class of so-called carriers; each of these had received previously extensive chemotherapy.

(d) *Sex.*—Patients of either sex received treatment without selection. The table reveals a sex distribution ratio of roughly three males to one female.

(e) *Age.*—Age alone was no bar to treatment, provided the diagnostic survey revealed no contraindications. The age limits varied from 16 to 56 years, with a mean age of 27 years.

(f) *Contacts.*—Whenever possible, all suspected "contacts" were examined bacteriologically and clinically. In addition to those found to be obviously infected, seven completely asymptomatic persons yielded positive cultures from secretions of the genital tract.

11. Desjardins, A. U.; Stuhler, L. G., and Popp, W. C.: Fever Therapy for Gonococcic Infections, J. A. M. A. 104: 873 (March) 1935.

12. Carpenter, C. M.; Boak, Ruth A.; Mucci, L. A., and Warren, S. L.: Studies on the Physiologic Effects of Fever Temperatures, J. Lab. & Clin. Med. 18: 981 (July) 1933.

13. Krusen, F. H.; Randall, L. M., and Stuhler, L. G.: Fever Therapy plus Additional Local Heating in the Treatment of Gonorrhea. Am. J. Syph., Gonorr. & Ven. Dis. 22: 185 (March) 1938.



## CARE OF THE PATIENT DURING HOSPITALIZATION

The technic by which the earlier treatments were carried out has been described in previous publications.<sup>14</sup> The changes which have accrued in our methods within the past two years have been described in detail elsewhere.<sup>15</sup>

All patients are hospitalized. Eligibility for fever therapy is determined after a thorough diagnostic survey, which includes a careful history, a complete physical examination and all indicated laboratory procedures. The apparatus employed was the hypertherm.

Most of the patients received a short preliminary "pilot" treatment, the purposes of which were to test the patient's physiologic responses to fever and to allay apprehension and to accustom him to lying in a warm, humid environment. The pilot treatment was given at a lower rectal temperature, usually 105 F., and was of three hours' duration. The last few patients included in this report received no preliminary pilot treatment. Their reactions, during and subsequent to the ten hour treatment, differed in no significant degree from those who also received the pilot treatment.

For the long treatment session the rectal temperature was elevated to 106.6 F. and was maintained at this level for either eight or ten hours. Throughout the treatment, except for brief rest periods, pure oxygen was supplied by means of the Boothby-Lovelace-Bulbulian<sup>16</sup> nasal mask in quantities sufficient to maintain an alveolar oxygen concentration of 60 per cent or more. At intervals of three hours the patient received 50 cc. of a 50 per cent solution of dextrose intravenously. No other fluids were given intravenously. He was encouraged to take by mouth 300 to 400 cc. an hour of iced 0.6 per cent solution of sodium chloride in tap water. The sedative used was pantopon<sup>17</sup> by hypodermic injection in doses of  $\frac{1}{6}$  to  $\frac{1}{3}$  grain (0.01 to 0.02 Gm.). Many patients required no sedative and few needed more than one such injection. The pulse rate seldom exceeded 130 beats per minute during the maintenance period and averaged 120 to 130 beats per minute. The cabinet doors were not opened except for intravenous injections, blood pressure recordings or checking the resistance wound rectal thermometer with a certified mercury thermometer. The constant inspection of the skin, which in former years was necessary to prevent burns, is unnecessary, since, with the low dry bulb temperatures now used, burns, are unknown and even erythema of a mild degree is not seen.

During each of the succeeding three days, the genital secretions were collected for smears and cultures. Cultures were made on two types of mediums: McLeod's<sup>18</sup>

medium and the plasma-agar medium developed by us.<sup>19</sup> During the past year only the latter medium was used. Culture mediums were incubated according to Thompson's<sup>20</sup> simplified technic for production of increased carbon dioxide tension. At the end of twenty-four hours the cultures were inspected and organisms from oxydase-positive<sup>21</sup> colonies were stained by Gram's method. If deemed advisable, a pure strain of the organism was isolated and its identity established by fermentation tests. An organism was accepted as being the gonococcus if it was a gram-negative diplococcus which grew poorly if at all on plain agar and which fermented only dextrose.

If the results of the bacteriologic examinations were negative for gonococci, the patient was dismissed and was then followed as an outpatient for at least three months.

## CRITERIA OF CURE

The term "cure" is employed in the bacteriologic as well as the clinical sense. The criteria of clinical cure in the male included complete resolution of the presenting clinical symptoms, absence of pus and shreds of mucus in the urine, restoration of the prostatic fluid toward normal, and failure of the usual "provocative" tests (massage of the periurethral glands over a urethral sound, and repeated prostatic massage) to influence the clinical status. It is our observation that little reliance can be placed on the clinical status alone in determining cure. Seven of the patients treated were asymptomatic from the outset, the diagnosis having been established solely on bacteriologic findings. Since the cultural methods employed have been so dependably accurate, we have relied chiefly on the bacteriologic findings in determining cure. Periodic cultural reexaminations of the genital secretions were carried out for a period of at least three months. In the female, pelvic examinations were done on the first postmenstrual day of each of the three menstrual periods following the treatment.

No patient was included in this series who had not been under observation for at least three months. A few of the patients were followed carefully for from two to two and one-half years.

## EXPERIMENTAL DATA

This series comprises a total of 83 patients who presented complications of gonorrhea and who were either presumably resistant or intolerant to sulfanilamide or to sulapyridine or to both drugs.

The different groups of patients were divided as follows:

## 1. Those receiving fever alone:

- (a) Eight hour sessions at 106.6 F.<sup>22</sup>
- (b) Ten hour sessions at 106.6 F.

## 2. Those receiving fever in combination with chemotherapy:

- (a) Ten hour sessions at 106.6 F. with oral sulfanilamide during eighteen hours before fever.
- (b) Ten hour sessions at 106.6 F. with intravenous sulfanilamide immediately before fever.

19. Rose, D. L.; Kendell, H. W., and Simpson, W. M.: A Plasma-Agar Medium for Cultivation of the Gonococcus, *Am. J. Clin. Path.* **10**: 59 (May) 1940.

20. Thompson, L.: A Simple Method of Supplying Carbon Dioxide in Jars for Bacteriological Cultures, *Am. J. Clin. Path.* **5**: 313 (July) 1935.

21. Gordon, J., and McLeod, J. W.: The Practical Application of the Direct Oxydase Reaction in Bacteriology, *J. Path. & Bact.* **31**: 185 (April) 1928.

22. All records of temperature refer only to rectal temperature, as determined by continuously operating electrical indicating thermometers.

14. Simpson, W. M.: Artificial Fever Therapy of Syphilis and Gonococcal Infections, *Brit. J. Ven. Dis.* **12**: 133 (July) 1936; Behandlung der Syphilis und der Gonorrhoea mit künstlich erzeugtem Fieber, *Wien. klin. Wchnschr.* **49**: 779 (June 19) 1936. Simpson, W. M., and Kendell, H. W.: Artificial Fever Therapy, *Colorado Med.* **34**: 782 (Nov.) 1937. Ruth, M. L.: Nursing Technic in Artificial Fever Therapy, *Ohio Nurses Rev.* **14**: 10 (Jan.) 1939.

15. Kendell, H. W.; Rose, D. L., and Simpson, W. M.: Fever Therapy Technic in Syphilis and Gonococcal Infections, *Arch. Phys. Therapy* **20**: 614 (Oct.) 1939.

16. Boothby, W. M.: Oxygen Administration: The Value of High Concentration of Oxygen for Therapy, *Proc. Staff Meet., Mayo Clin.* **13**: 641 (Oct. 12) 1938. Lovelace, W. R.: Oxygen for Therapy and Aviation: An Apparatus for the Administration of Oxygen or Oxygen and Helium by Inhalation, *ibid.* **13**: 646 (Oct. 12) 1938. Bulbulian, A. H.: Design and Construction of the Masks for the Oxygen Inhalation Apparatus, *ibid.* **13**: 654 (Oct. 12) 1938.

17. A preparation of the hydrochlorides of the alkaloids of opium, principally morphine.

18. McLeod, J. W.; Coates, J. C.; Hapgood, J. C.; Priestley, D. P., and Wheatley, B.: Cultivation of the Gonococcus as a Method in the Diagnosis of Gonorrhea, with Special Reference to the Oxydase Reaction and to the Value of Air Reinforced in Its Carbon Dioxide Content, *J. Path. & Bact.* **39**: 221 (July) 1934.

(c) Ten hour sessions at 106.6 F. with concomitant Promin.

(d) Ten hour sessions at 106.6 F. with Promin during eighteen hours before fever.

1. (a) *Those Receiving Eight Hour Sessions of Fever Alone.*—This group comprises 9 patients. As shown in the table, only 1 patient in this group was bacteriologically negative following a single eight hour session at 106.6 F. The number of such treatments required to effect cure in this group averaged two and four tenths. Although considerably better than the average of four and eight tenths five hour sessions during the presulfanilamide era,<sup>23</sup> this plan of treatment did not appear to possess the merit of the longer ten hour sessions and was abandoned in favor of the latter.

(b) *Those Receiving Ten Hour Sessions of Fever Alone.*—The treatment of patients in this group followed the same plan as that described previously with the exception that ten hours instead of eight hours of fever at 106.6 F. were given. The results, as shown in the table, indicate that 10 of the 16 patients (62.5 per cent) recovered from the infection following a single ten hour session at 106.6 F. The average number of such treatments required was one and fifty-six one hundredths. Even though these patients may have received an adequate total dose of sulfanilamide prior to hospitalization, it could be argued that they were not necessarily sulfanilamide resistant, since either insufficient individual doses or failure to give the drug during the night would militate against an effective sustained blood (and tissue) concentration. For this reason an unselected group of 5 consecutive patients, all of whom were believed to be resistant to sulfanilamide, were hospitalized. Sulfanilamide was then given under strictly controlled conditions in the dosages recommended by Long and Bliss.<sup>23</sup> A sufficient amount of this drug was given to maintain the blood sulfanilamide level between 10 and 12 mg. per hundred cubic centimeters for a period of ten days. The dosage employed varied but averaged 20 grains (1.3 Gm.) every four hours, or a total of 120 grains (8 Gm.) daily. At the end of this period the 5 patients still presented active clinical symptoms of gonorrhea, and the genital secretions were bacteriologically positive for *Neisseria gonorrhoeae*. These patients were then given ten hour sessions of fever at 106.6 F. and are included in the total of the 16 patients comprising this group. It is worthy of mention that, despite the careful maintenance of the blood sulfanilamide concentration at a high level for an extended period of time, as a group these patients were no more susceptible to fever than those who had not received such intensive, controlled medication; one and eight-tenths ten hour sessions were required to effect cure in this group as compared with one and forty-five one hundredths similar sessions for others in the ten hour group.

2. (a) *Those Receiving Ten Hours of Fever Combined with Oral Sulfanilamide During Eighteen Hours Before Fever.*—Since there seemed to be no virtue in an intensive ten day course of sulfanilamide prior to fever, this procedure was abandoned. Wengatz, Boak and Carpenter<sup>24</sup> and Warren have shown that in the presence of a concentration of 1:10,000 of sulfanilamide the thermal death time of a given strain of gonococcus was lowered approximately 50 per cent. An attempt

was made in this group of patients to apply this principle by the application of artificial fever at a time when a 1:10,000 concentration (10 mg. per hundred cubic centimeters) of sulfanilamide was present in the body.

This group consists of 20 unselected patients of the same type as that comprising the preceding series. The comparison of this group with those groups receiving fever alone is shown in the table.

All received the same type of treatment as that which has been described previously with one exception: Beginning at 2 p. m. on the day following the pilot treatment, sulfanilamide was given by mouth. The initial dose for persons weighing over 150 pounds (68 Kg.) was 80 grains (5.2 Gm.); for persons weighing less than 150 pounds, 60 grains (4 Gm.) was given. Thereafter, at intervals of four hours, maintenance doses, each of 20 grains (1.3 Gm.), were given. Thus, a total of 140 (9 Gm.) or 160 (10 Gm.) grains of the drug was given over a period of eighteen hours in five doses. The blood sulfanilamide concentration, as determined by the method of Marshall,<sup>25</sup> or, more recently, by the method of Bratton and Marshall<sup>26</sup> as adapted to the Sheard-Sanford "photometer,"<sup>27</sup> averaged 12 mg. per hundred cubic centimeters at the time the patient was placed in the cabinet. Starting at 7 o'clock the following morning, eighteen hours after the administration of sulfanilamide was begun, the patients received a ten hour session of fever at 106.6 F. No additional sulfanilamide was given.

The results in this group were much more encouraging. No patient demonstrated clinical or bacteriologic evidence of gonococcal infection after the single ten hour session of fever when the blood sulfanilamide concentration had been elevated to from 10 to 12 mg. per hundred cubic centimeters at the commencement of the fever session. The sulfanilamide concentration of the blood at the conclusion of the ten hour fever treatment averaged 8 mg. per hundred cubic centimeters. It may be assumed, therefore, that a 1:10,000 concentration of sulfanilamide was present in the tissues for at least the greater part of the ten hour session and would seem to lend some support to the conclusions of Wengatz and his co-workers<sup>24</sup> as far as it is possible to make an analogy between in vitro and in vivo experiments.

From the practical standpoint, however, we were not satisfied with this program. The amount of sulfanilamide given during the eighteen hours preceding the fever treatment appeared to have a definite influence on the patients' reactions during the treatment. The actual amount of fever administered was the same as that given to those patients who had received no sulfanilamide. Hence any changes exhibited by the patient could reasonably be attributed only to the drug.

Since it was necessary to administer the drug at frequent and regular intervals during the day and night, it was customary for patients to report to the fever therapy department with the complaint that they had had little or no sleep during the night. Consequently the patient was relatively exhausted before the fever treatment was started. This was undesirable, since it had been found that those patients who were well rested when they came to the long treatment

23. Long, P. H., and Bliss, Eleanor A.: The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds, New York, Macmillan Company, 1939.

24. Wengatz, H. F.; Boak, Ruth A., and Carpenter, C. M.: The Bactericidal Effect of Sulfanilamide on the Gonococcus in Vitro. *J. Bact.* 35: 36 (Jan.) 1938.

25. Marshall, E. K.: Determination of Sulfanilamide in Blood and Urine. *J. Biol. Chem.* 122: 263 (Dec.) 1937.

26. Bratton, A. C., and Marshall, E. K.: A New Coupling Component for Sulfanilamide Determination. *J. Biol. Chem.* 128: 537 (June) 1939.

27. Sanford, A. H.; Sheard, C., and Osterberg, A. E.: The Photometer and Its Use in the Clinical Laboratory. *Am. J. Clin. Path.* 3: 405 (Nov.) 1933.

tolerated the treatment much more readily than those who were fatigued. The unfortunate tendency of sulfanilamide to produce nausea and occasional vomiting was evident in all of these patients. Thus, in addition to being more or less exhausted the patient was also nauseated, and often vomiting, before the fever session was begun. Almost without exception they also exhibited the bluish discoloration of the skin and mucous membranes characteristic of persons receiving sulfanilamide. This circumstance made it difficult to judge the state of oxygenation of the blood during the subsequent fever period by the appearance of the skin and mucous membranes. Finally, the known tendency of sulfanilamide also to produce dizziness, headache, mild mental confusion and delirium was definitely exaggerated at a temperature of 106.6 F.

Therefore, without denying that such a combined form of chemical and fever treatment was highly effective therapeutically, a method was sought to attain the same result without the presence of these annoying side complications.

(b) *Those Receiving Sulfanilamide Administered Intravenously Immediately Before Fever.*—Sixteen patients are included in this group, the results of whose treatment are shown in the table. The pretreatment medication schedule of these patients was as follows: The patient was permitted to rest the day and night preceding the long treatment. One hour before the ten hour fever session, sulfanilamide was given intravenously in the form of an 0.8 per cent solution (in physiologic solution of sodium chloride), the dosage being calculated on the basis of  $\frac{3}{4}$  grain (0.05 Gm.) per pound of body weight. The solution was prepared immediately prior to administration. The actual amount of sulfanilamide thus given was somewhat less than that which is given orally to patients of group 2a. Such dosage was sufficient to produce blood sulfanilamide concentrations of 10 mg. or more per hundred cubic centimeters of blood for the duration of the fever treatment. The administration of the drug one hour before the fever treatment was thought to allow sufficient time for its complete distribution throughout the fluids of the body.<sup>28</sup>

From the practical standpoint, such a program appeared to remove the difficulties inherent in the oral method of administration of the drug. Toxic reactions were strikingly diminished and in many patients were completely absent. Since the amount of fever administered to the two groups was exactly the same, the type of patient was the same and the blood sulfanilamide concentrations were practically identical in the two groups, we anticipated that the therapeutic results would be comparable. This did not prove to be the case.

Of these 16 patients, only 13 were cured by the single ten hour fever session combined with sulfanilamide given intravenously. Even with due regard to the small number of patients included in either group, the differences seemed to be statistically significant. We were therefore forced to the conclusion that the mere presence of sulfanilamide in a 1:10,000 concentration at the time the fever was given does not wholly explain its therapeutic action and hence that the *in vitro* experiments of Wengatz and his associates could not be translated directly to *in vivo* conditions.

(c) *Those Receiving Fever Combined with Promin During the Treatment.*—Promin,<sup>29</sup> the sodium salt of p,p'-diaminodiphenylsulfone-N,N'-di (dextrose sulfonate), differs from other similar compounds in its high degree of solubility. It is prepared as a stable 40 per cent aqueous solution which is suitable for parenteral injection. Because of its extreme solubility, it is possible to administer relatively large quantities of the drug in a minimum amount of solvent. For example, 5 Gm. of Promin may be administered in a total solution volume of 12.5 cc. Furthermore, because of such ready solubility in aqueous fluids, it was thought that diffusion in the body fluids should be more rapid and complete than is the case with sulfanilamide.

Its therapeutic efficacy, particularly in the treatment of gonococcic infections, was largely undetermined. Therefore a series of patients were subjected to the same type of experimental program as that described under group 2b with the exception that, instead of sulfanilamide being administered immediately prior to the treatment, 5 Gm. of Promin was injected intragluteally when the fever treatment was started and every three hours during the treatment. Thus a total of 20 Gm. of the drug was given during the ten hour session of fever. Blood Promin concentrations, determined by a suitable adaptation of the method of Bratton and Marshall,<sup>30</sup> averaged from 10 to 15 mg. per hundred cubic centimeters for the duration of the treatment. Excretion of the drug following the treatment appeared to be very rapid, since only traces could be found in the blood from twelve to sixteen hours later.

With the exception of a moderate degree of irritation at the site of injection, which disappeared within twenty-four hours, this compound was uniformly well tolerated. The toxic reactions common to sulfanilamide were not observed. In a minority of the patients, toward the end of the fever session a mild degree of "cyanosis" of the skin and mucous membranes was evident. There was no dizziness, confusion, headache, gastrointestinal upset or other sign of toxicity of the type commonly observed following the oral administration of sulfanilamide.

Of the group of 11 patients with refractory gonococcic infection subjected to this program, only 7 were cured following a single fever session of ten hours at 106.6 F. Therefore it was felt that there were no advantages in the concurrent use of Promin and fever therapy, as administered to these patients, over fever therapy alone.

(d) *Those Receiving Ten Hours of Fever Combined with Promin During Eighteen Hours Before Fever.*—Since Promin is known to be an effective compound<sup>30</sup> and because we had observed an apparent potentiation of the action of sulfanilamide when administered during a period of eighteen hours prior to fever, a final experiment was designed to test the hypothesis that Promin likewise might be more effective when administered for a definite period before the fever session.

The schedule of Promin administration in this group was as follows: Beginning at 2 o'clock on the afternoon preceding the long treatment session and at intervals of four hours thereafter, the patient received 5 Gm. injections of Promin intramuscularly. Thus a total of 25 Gm. of the compound was given during the eighteen hour period prior to the fever treatment. None was given during the fever session.

28. Painter, E. E.: The Application of Spectrographic Methods to the Determination of Total Body Water with Sulfanilamide, in Proceedings of the Sixth Summer Conference on Spectroscopy and Its Application, Massachusetts Institute of Technology, 1939, p. 125.

29. Promin was supplied by Dr. E. A. Sharp, director of clinical investigation, Parke, Davis & Co., for investigative purposes.

30. Greer, P. H.; MacLaren, D. B., and Lucas, C. C.: Comparative Chemotherapy in Experimental Pneumococcal Infections, *Canad. M. A. J.* 40: 319 (April) 1939.

The blood Promin concentrations at the beginning of the treatment were considerably higher than those noted in the preceding group of patients, although excretion of the drug appeared to be more rapid. The initial concentration of the drug in the blood averaged 23 mg. per hundred cubic centimeters; at the conclusion of the treatment it averaged 7 mg. per hundred cubic centimeters.

Signs of toxicity were minimal. A noticeable degree of the bluish discoloration of the skin and mucous membranes was present in all of these patients, comparable to that produced by sulfanilamide. In the majority of cases a definite methemoglobin band could be detected on spectroscopic examination of the blood. Despite the necessity for awakening the patient during the night to administer the drug, the complaint of insomnia was practically absent. Headache, nausea, dizziness, confusion and delirium were not encountered. Of special interest was the almost complete absence of the post-fever depression customarily seen the day following the long treatment session in those persons receiving sulfanilamide.

The therapeutic efficacy of this type of treatment, as measured by cure following the single session of ten hours of fever at 106.6 F., compares favorably with that noted in group 2a. All of the 11 patients in this group were cured following the single long treatment. If this high degree of therapeutic efficacy can be maintained, it would appear that this is the treatment of choice.

#### COMMENT

It is felt that these observations provide at least a partial answer to a number of pertinent questions which have been raised regarding the treatment of gonococcal infections. One of the first queries concerned the possibility that resistance to chemotherapy might also be paralleled by resistance to other forms of therapy, including artificial fever. It has been reported<sup>31</sup> that, in those cases in which sulfanilamide has failed to cure, fever therapy has been equally ineffective. Our experiences indicate that there is no correlation between variations in chemolability and in thermolability. The amount of fever necessary to effect cure in those patients who received fever therapy alone included in Groups 1a and b closely approximates that reported<sup>13</sup> in the pre-sulfanilamide era.

Artificial fever combined with chemotherapy has been reported<sup>6</sup> to be highly effective in the treatment of gonococcal infections. The occurrence of drug fever during the course of sulfanilamide medication has also been noted<sup>32</sup> to cause a definite shortening of the course of the disease.

The role of artificial fever combined with chemotherapy in those cases resistant to the drug alone has not been well defined. Elkins and Krusen<sup>33</sup> have reported that in forty-three cases of sulfanilamide-resistant gonorrhea an average of one and two-tenths ten hour sessions at 106.6 F. has effected cure with sulfanilamide given in daily dosages of 80 grains (5.2 Gm.) for two days preceding the fever treatment. Owens, Wright and Lewis<sup>34</sup> have reported that 4 patients with sulfanilamide-resistant gonorrhea were cured by a single fever

treatment when they were given "large doses of sulfanilamide for three or four days and then, when they had attained the usual saturation with the drug, giving them the ten hour fever treatment." Belt and Folkenberg,<sup>35</sup> in a series of 49 patients with refractory gonococcal infections, were able to effect cure in 86 per cent by the combination of artificial fever and chemotherapy.

The interesting variation in therapeutic effectiveness in the two modes of administration of sulfanilamide presented in this report raises several important questions. Is the difference in effectiveness related to blood concentration alone? In general, those patients receiving sulfanilamide intravenously attained somewhat higher concentrations than those receiving the drug orally. Indeed, in several patients in group 2a the blood level was only approximately one-half the average for the group as a whole; yet these patients responded no differently than did those possessing higher blood concentrations. In the literature, furthermore, there is no general agreement as to what constitutes the maximum effective blood concentration; from 1 to 2 mg. per hundred cubic centimeters has been reported<sup>36</sup> to be as effective experimentally as 10 mg. per hundred cubic centimeters.<sup>33</sup> Perhaps this discrepancy may be explained on the basis of the observation<sup>37</sup> that there is no correlation between resistance of a given strain of gonococcus to sulfanilamide *in vivo* and its behavior in a test tube. If this observation is essentially correct, it might also indicate that the therapeutic difference between groups 2a and 2b may be due neither to a lowering of the thermal death time, as the work of Wengatz would suggest, nor to a thermal potentiation of the bactericidal action of sulfanilamide, as the work of White<sup>38</sup> would imply.

Is the difference one of relative rather than actual resistance to sulfanilamide? A growing body of evidence has accumulated which indicates that it is possible to produce drug-fast strains of gonococci *in vivo*<sup>2</sup> during the course of chemotherapy, a type of resistance which appears to be "permanent" (i. e., it persists in subcultures). Providing some support to this theory is the small number of patients included in group 1b, in which a ten day period of intensive sulfanilamide therapy failed to influence the course of the disease either bacteriologically or clinically. In this connection it may also be stated that at no time during this ten day period was there any difficulty in cultivating the gonococcus from the genital secretions, nor did there appear to be any tendency toward the appearance of atypical forms of the organism.

The mere presence of sulfanilamide alone does not completely explain its action, as the results of the treatment of the patients in group 2b demonstrate. We therefore incline to the opinion that, during the eighteen hour period of administration of the chemotherapeutic agent prior to fever therapy, potentiation of some factor within the body occurs; whether this is in the direction of stimulation of the body's defensive mechanisms or is in the nature of attenuation of the offensive mechanism of the gonococcus is not clear. The available evi-

31. Crenshaw, J. L., and Cook, E. N.: Limitations, Dangers and Failures of Sulfanilamide in Treatment of Urinary Tract Infections, *J. Urol.* **41**: 64 (Jan.) 1939.

32. Lich, R., and Rowntree, G. R.: Sulfanilamide Therapy in Acute Neisserian Urethritis, *Am. J. Syph., Gonorr. & Ven. Dis.* **23**: 323 (May) 1939.

33. Elkins, E. C., and Krusen, F. H.: Clinical Results of Fever Therapy, *Arch. Phys. Therapy* **20**: 346 (June) 1939.

34. Owens, C. A.; Wright, W. D., and Lewis, M. D.: The Value of Fever Therapy in Sulfanilamide-Resistant Gonorrhea, *J. Urol.* **40**: 847 (Dec.) 1938.

35. Belt, A., and Folkenberg, A. W.: Treatment of Gonorrhea by Artificial Fever Alone and in Combination with Sulfanilamide, *Arch. Phys. Therapy* **21**: 203 (April) 1940.

36. Osgood, E. E., and Brownlee, I. E.: Culture of Human Marrow: Studies on the Mode of Action of Sulfanilamide, *J. A. M. A.* **110**: 349 (Jan. 29) 1938. Finkelstein, R., and Birkeland, J. M.: Mode of Action of Sulfanilamide and Protosil, *Science* **87**: 441 (May 13) 1938.

37. Cohn, A.; Jacoby, A.; Kornblith, B. A., and Wishegrad, M.: A Clinical and Experimental Evaluation of Sulfanilamide in Gonorrhea, *Am. J. Syph., Gonorr. & Ven. Dis.* **23**: 41 (Jan.) 1939.

38. White, H. J.: The Relationship Between Temperature and the Streptococcal Activity of Sulfanilamide and Sulfapyridine *In Vitro*, *J. Bact.* **38**: 549 (Nov.) 1939.

dence concerning the bacteriostatic nature of the action of the drug would seem to support the latter thesis.

Finally, the public health implications of such a highly effective method of treatment should not be overlooked. The ultimate goal in the control of venereal diseases should be methods which will quickly and surely eliminate the infection. With such a therapeutic system as that outlined in the text of this paper, combined with adequate case-finding methods for the purposes of discovering and treating "contacts," the venereal disease control program advocated by the U. S. Public Health Service could be achieved in a much shorter time and with greater assurance of actual cure than by present day methods.

#### CONCLUSIONS

1. Eighty-three patients suffering from complications of gonorrhea, resistant or intolerant to chemotherapy, have been treated with artificial fever, either alone or combined with chemotherapy.

2. Of those refractory patients receiving fever therapy alone, only 12.5 per cent were cured following a single eight hour treatment at 106.6 F.; 62.5 per cent were cured following a single ten hour treatment at 106.6 F.

3. When combined with artificial fever, the effectiveness of chemotherapy (sulfanilamide or Promin) is influenced by the time-dosage relationship with respect to the fever treatment; when administered for eighteen hours preceding the fever treatment, the effectiveness is much greater than when administered immediately prior to or during the treatment.

4. A ten day period of intensive sulfanilamide therapy prior to fever therapy is without value in sulfanilamide-resistant patients, provided none of the drug is present in the body fluids at the time of the fever treatment.

5. All of 31 unselected consecutive patients treated with sulfanilamide or Promin for eighteen hours before a single ten hour fever session at a rectal temperature of 106.6 F. were cured.

6. Rigid bacteriologic criteria were employed as the chief basis for the determination of cure.

7. The combination of a single ten hour session of artificial fever therapy combined with the administration of adequate sulfanilamide or Promin for eighteen hours prior to the fever treatment appears to be the procedure of choice in the treatment of chemotherapy-resistant gonococcal infections.

---

**Diphtheria and Acute Tonsillitis.**—There is a striking contrast between the onset of an attack of acute tonsillitis and an attack of diphtheria. Tonsillitis begins explosively with a chill, high fever, nausea, vomiting, headache, backache and a fiery red and swollen throat, which renders swallowing an exceedingly painful act. The victim is obviously very ill from the start. . . . Diphtheria, however, does not announce itself in any such dramatic manner. It begins after an incubation period of from one to five days, with a little fretfulness and lassitude. The favorite games and toys no longer interest. The appetite is capricious, but since swallowing is performed without difficulty, and since there is no change in the voice nor complaint of sore throat, the possibility of diphtheria is not suspected by the average parent. The mouth temperature at this stage is only slightly above normal, rarely more than 100 or 101 F., and this serves further to allay suspicion. The diagnosis of diphtheria should not be discarded, however, because the temperature is higher than 101 F.—Holmes; William H.: *Bacillary and Rickettsial Infections—Acute and Chronic*, New York, Macmillan Company, 1940.

## ANORECTAL OPERATIVE PROCEDURES WITH SPECIAL REFERENCE TO THE AVOIDANCE OF PAIN

BASED ON A SERIES OF ONE THOUSAND CASES

HARRY E. BACON, M.D.

PHILADELPHIA

A statistical report recently published by a large insurance company gives the incidence of hemorrhoidal disease as one fifteenth of the total population of the United States. If these individual case records were carefully studied it is highly probable that many allied conditions of the anorectum were included in the original survey. In part, at least, this report gives evidence of the frequency of the disease. It is not my purpose in this presentation to discuss the prevention of hemorrhoidal disease although it may be said that much has been accomplished in respect to education of persons, especially the young, as to the value of a regular daily evacuation, a well balanced diet, the avoidance of drastic cathartics and periodic complete examination.

For treatment, conservative measures may be employed with satisfaction, but in the vast majority of anorectal disorders surgical intervention is required. Rectal operations enjoy an unenviable reputation for postoperative pain among both physician and the laity, and unfortunately this reputation is not altogether unfounded. The important question is, why do patients experience such severe pain and what measures can be taken for its prevention or decrease? The abundant nerve supply to the lowermost portion of the intestinal tube (anal canal) and perianal areas, which is derived from the somatic portion of the cerebrospinal nervous system, accounts for its marked sensitivity; therefore, distress of varying intensity incidental to surgical trauma is physiologic. Of utmost importance, however, is the contraction of the voluntary anorectal muscles, especially the external sphincter, which is so frequently associated, giving rise to that which is termed "sphincter spasm." Of course, above the anorectal line (union of rectum with anal canal) the innervation is sympathetic and parasympathetic.

Largely through the efforts of proctologists here and abroad, constant progress has been made toward rendering the postoperative course less painful through the injection of oil-soluble anesthetics. All will agree that their use, while of advantage and to be advocated, is inadequate. Is it not consistent with sound reasoning that the operative factors influencing the degree of pain be considered as well as the relief?

Pain postoperatively, immediate and remote, is due largely to spasmodic contraction of the external sphincter muscle. A careful analysis of each case in several large series revealed that this "sphincter spasm" was due not to one but to many factors, namely unnecessary trauma to the tissues accentuated by inhalation anesthetics; failure to respect the continuity of the anorectal juncture and to preserve adequate anal and adjacent perianal skin; inclusion of the external sphincter muscle, wholly or in part, in the suture or clamp; omission of one of the prolonged aqueous analgesic solutions; the employment of the usual abusive whistles or packs, and improper as well as inadequate after-care. With

---

From the Departments of Proctology, Temple University and Post-Graduate School of Medicine, University of Pennsylvania.

Read before the Section on Gastro-Enterology and Proctology at the Ninety-First Annual Session of the American Medical Association, New York, June 13, 1940.

this in mind, I recommend the operative procedures on an anatomic basis and according to the pathologic condition present.

During the four year period ending February 1940 operation has been performed on 1,033 patients, which number includes only those procedures commonly asso-

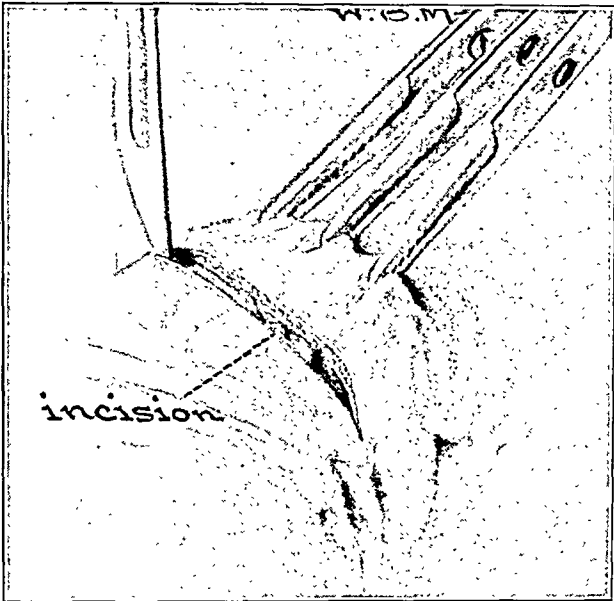


Fig. 1.—Incision in skin high on lateral wall of the hemorrhoid, beginning at the anorectal line.

ciated with pain. While it can be frankly stated that no one group of persons was absolutely free of pain, and even though the problem of absolute relief is far from its solution, the results have been so favorable and encouraging that I take this opportunity of reporting my experience.

For the purpose of brevity and because radical hemorrhoidectomy is rightly to be considered the most painful procedure on the anorectum, only this technic is

TABLE 1.—Dosage of Analgesic Solution

Weight in Pounds	Dose in Mg.	Lumbar Interspace
70 - 100.....	40	4th
101 - 150.....	50	4th
151 - 170.....	60	4th
171 - 190.....	70	4th
191 - 210.....	80	4th
211 - 220.....	90	4th
221 - 240.....	100	4th

described. The preoperative sedation and anesthetic, and the postoperative care differ but little with the various surgical procedures. Strict adherence to every detail is essential. The procedure is as follows: The patient is hospitalized the night prior to operation; an enema of physiologic solution of sodium chloride is administered through a small rubber catheter, and pentobarbital sodium, 1½ grains (0.09 Gm.), is given by mouth. The following morning the perineum and lumbosacral regions are closely shaved and prepared. In addition to the usual physical examination, the blood pressure readings are made of both arms and the weight of the patient tabulated. Complete blood cell count, blood chemistry and urinalysis are routine procedures. The second and first hour before operation, pentobarbital sodium in 1½ grain (0.09 Gm.) doses is given by mouth.

*Analgesia.*—Low lumbar (spinal), sacral, caudal, combined or conduction analgesia is employed. In the series of patients previously cited, approximately 90 per cent were given a block low in the lumbar region, the dose of the analgesic solution being determined by the body weight of the patient.

For the purpose of sustaining blood pressure during operation, neosynephrin hydrochloride according to the preoperative pressure with procaine hydrochloride is injected into the fourth lumbar interspace.

*Surgical Technic.*—With the patient in the jack-knife or inverted position, the sphincter muscles are gently massaged and the anorectum is cleansed. The gloves

TABLE 2.—Dosage of Neosynephrin Hydrochloride

Systolic Blood Pressure, Left Arm	Dosage of Neosynephrin Hydrochloride
131 to 140.....	0.1 cc. in 1 cc. 0.5% procaine hydrochloride
121 to 130.....	0.2 cc. in 1 cc. 0.5% procaine hydrochloride
111 to 120.....	0.3 cc. in 1 cc. 0.5% procaine hydrochloride
101 to 110.....	0.4 cc. in 1 cc. 0.5% procaine hydrochloride
90 to 100.....	0.5 cc. in 1 cc. 0.5% procaine hydrochloride

used for the analgesia and gentle divulsion are discarded. The operator dons sterile gown and gloves, and the perianal region is prepared. After appropriate drapes are in place, the hemorrhoidal masses are drawn outside the anus in their respective quadrants by means of curved Rankin hemostats. Additional hemostats are applied to the hemorrhoid to bring into view as much hemorrhoidal tissue as possible without undue tension. Where external hemorrhoids are present, a small elliptic incision is made high on the lateral side of each beginning at a point just distal to the anorectal line and

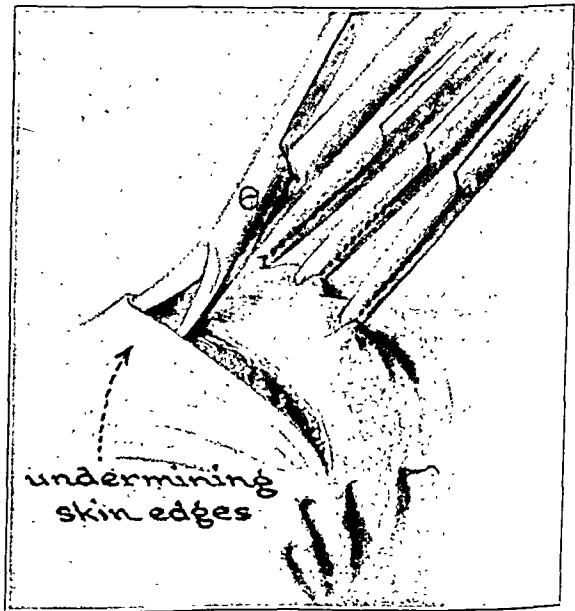


Fig. 2.—By means of small curved scissors the subcutaneous veins are separated for preservation of the skin.

carried to a point one-half inch beyond the tip of the external hemorrhoidal mass. The outer leaf of skin on each side of the hemorrhoid is elevated with fine tissue forceps and separated from the underlying tissue by means of small blunt-tipped curved scissors. The hemorrhoid is elevated, and blunt dissection is begun at the apex where the two incisions are joined. The



adjacent veins, which have been freed on either side, are drawn medially by an assistant, and the operator continues with the blunt dissection on the surface of the external sphincter muscle. When the inner edge of this muscle is encountered, a small right angle retractor is placed so as to draw the muscle gently from the field

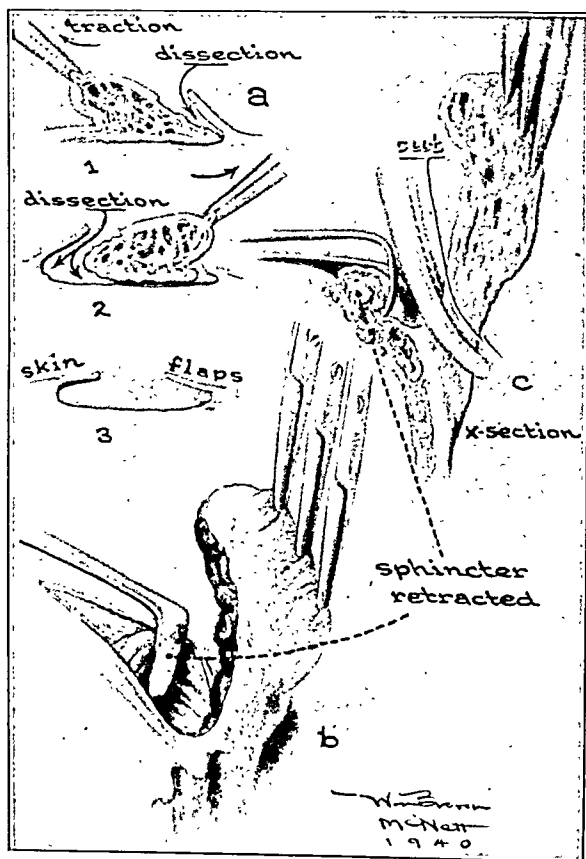


Fig. 3.—a 1, manner in which the subcutaneous veins and tissue are separated from anal and perianal skin; a 2, posterolateral wall similarly treated; a 3, wound after hemorrhoid and all subcutaneous veins have been freed and drawn medialward. b, the hemorrhoid and subcutaneous veins have been dissected free on and above the surface of the external sphincter muscle and the latter is retracted. c, muscle retractor in place; Smith clamp applied in longitudinal axis. Arrow shows line of incision.

of operation. A Smith hemorrhoidal clamp is placed on the hemorrhoidal mass in the longitudinal axis of the bowel and the hemorrhoid cut away. A suture of no. 0 chromic catgut or no. 00 pyoktannin on a no. 12 Ferguson needle is introduced  $\frac{1}{4}$  inch (0.64 cm.) from the tip of the clamp and tied—the free end to serve as an anchor. The base of the hemorrhoid is then sutured beneath the clamp from side to side. As the anorectal line is approached, the hemorrhoidal clamp is removed and the sphincter muscle permitted to return to its usual location. A subcutaneous bed is formed by continuing the suture to the outer limit of the apex. After all hemorrhoidal masses are treated in a similar fashion, the skin may be approximated distally by means of two or three interrupted sutures of black silk or number 35 alloy steel wire. Where the latter is employed, only a single knot is tied. Ten cc. of a 0.5 solution of diothane hydrochloride is distributed into the substance of the sphincter muscle through a single puncture in the posterior midline behind the anal verge. A cellophane tube drain, of 4 inch no. 14 soft rubber tubing surrounded by a strip of wet cellophane, is introduced, and dressings are applied.

**Postoperative Care.**—Immediately on the patient's return to his room, the foot of the bed is elevated for six hours where a hypobaric (light) analgesic solution is used intraspinaly. Liquids, a light soft diet and smoking are permitted. Compresses wrung out in hot boric solution are applied continuously. At night these may be supported by a hot water bottle. Morphine sulfate in  $\frac{1}{4}$  grain (0.01 Gm.) doses is given only if necessary. Blood pressure readings are made every hour for six hours in both arms. Twenty-four hours after operation the cellophane tube drain is removed and an aqueous solution of 1 per cent gentian violet applied on a glass rod. Liquid petrolatum is given by mouth once or twice daily and continued for approximately ten to fourteen days. On the second postoperative day, an enema of warm saline solution or olive oil is administered through a no. 14 soft rubber catheter. Thereafter the patient is permitted out of bed, a house diet is prescribed and sitz baths thrice daily, at a temperature of 110 F. and a depth of 6 inches for ten minutes, are begun. When discharged on the third or fourth postoperative day, the patient is advised to continue with the sitz baths, employ cotton tissue rather than toilet paper and have one daily evacuation. Skin sutures are removed on the fifth to the seventh day, at which time the lubricated gloved finger is introduced.

**Analysis of Cases.**—The degree of postoperative pain in this series was determined by several factors: (a) subjective complaint, (b) narcotic required, (c) ease of first bowel movement, (d) need for catheterization and (e) digital examination.

Ten hundred and thirty-three operative procedures in the hospital on adults were performed, of which 642 were for hemorrhoids. However, in 416 cases the method of hemorrhoidectomy previously outlined was utilized, and only 32 patients, or 7.6 per cent, complained of severe pain. This number required a mini-

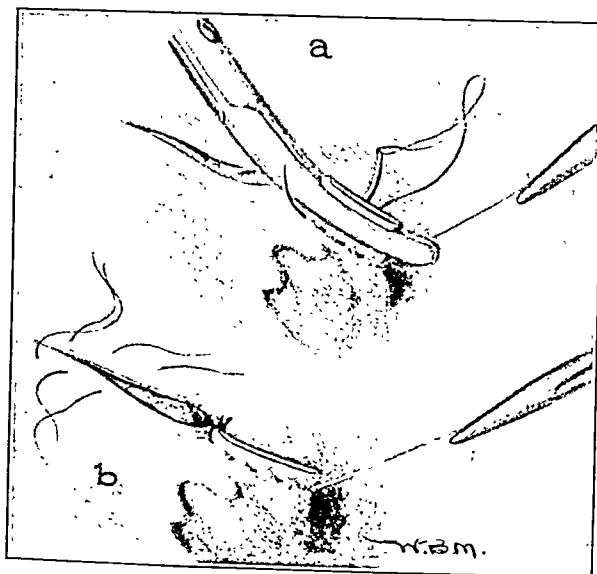


Fig. 4.—a, anchor suture placed in mucosa immediately above excised internal hemorrhoid. Suture continued beneath the clamp to anorectal line when clamp is removed. Subcutaneous bed beneath anal and perianal skin is continued. b, distal portion of skin is approximated with black silk or number 0.35 alloy steel wire.

mum of two and a maximum of three  $\frac{1}{4}$  grain (0.01 Gm.) doses of morphine. It may be mentioned that 14 of this group were members of the medical profession. Forty-one per cent of the patients complained of considerable discomfort during the first twenty-four

hours, for which a single dose of the narcotic was given. The remaining number, 51.4 per cent, cited discomfort but no pain such as necessitated a narcotic. In the entire group, many patients were restless and insomnolent, for which reason pentobarbital-sodium was prescribed, but no estimation of the number was made. On no occasion did a patient describe pain on removal of the cellophane tube.

Only 12 per cent of the patients in whom a fissure was excised complained of pain; this group required one dose of morphine,  $\frac{1}{4}$  grain (0.01 Gm.).

Considering now the entire group of 1,033 cases, 27 per cent cited pain as such and required a narcotic during the first twenty-four hours; 2 per cent were given morphine the second day. About one-half the number received castor oil by mouth on the third postoperative day, and while accurate statistics have not been completed, practically all experienced moderate to severe pain at the time of the first evacuation. Since a warm saline or olive oil enema through a small soft rubber catheter has been substituted, usually on the second postoperative day, no pain was cited, although varying degrees of discomfort were described at subsequent voluntary movements. The patient, however, being permitted out of bed, sat in hot water immediately.

Urinary retention in a series of 1,126 cases recently reported was computed at 7.1 per cent (81 patients). All, however, did not require catheterization.

Digital examination from the second to the seventh postoperative day was attended by varying degrees of discomfort. No complications, such as abscess formation, from closure of the wound in the perianal skin were encountered, although in each case dead-spacing was prevented by the formation of a subcutaneous bed. The cutaneous wound in most instances healed by first intention, especially where alloy steel wire was employed. The period of convalescence hemorrhoidectomies, including those of the external variety, averaged nineteen days. Worthy of special mention is the fact that almost all patients, exclusive of those for whom a plastic procedure on the sphincter was performed, showed some degree of sphincter muscle atonia, averaging five to eight days. One patient, on whom a hemorrhoidectomy was done, was examined on the fifty-first postoperative day and cited lack of control. The muscle was atonic. When he was seen one week later, the tone had returned to normal. In the gross series, the period of hospitalization postoperatively averaged four and one-fourth days.

#### SUMMARY AND CONCLUSIONS

1. Spasmodic contraction of the external sphincter muscle is the important factor in the production of pain.
2. An improved technic of hemorrhoidectomy without trauma to the external sphincter muscle was adopted, based on a series of 416 cases. Of this number, 51.4 per cent cited discomfort but no pain and did not require a narcotic.
3. In the entire series of 1,033 patients only 27 per cent cited pain as such and required a narcotic.
4. Contrary to common belief, wounds of the skin may be sutured without complications, providing a subcutaneous bed is formed. By this method the period of convalescence is reduced.
5. The prolonged use of an analgesic solution has proved of value in this series toward the avoidance of sphincterismus.
6. Meticulous postoperative care and periodic examination thereafter are to be recommended.

1527 West Girard Avenue.

#### ABSTRACT OF DISCUSSION

DR. EMIL GRANET, New York: Freedom from postoperative complications and pain depends primarily on technics designed to minimize trauma and infection. For proctologic surgery, epidural caudal block utilizing 30 to 40 cc. of 2 per cent procaine hydrochloride has given ideal anesthesia. Twelve per cent were failures resulting from anatomic abnormalities which prevented adequate deposition of the anesthetic solution. The disagreeable complications of spinal anesthesia, such as headache, vomiting and hypotension, as well as late neurologic sequelae recently described by Brock and others, are avoided by epidural anesthesia. The inverted angle position is comfortable for patient, operator and assistant. The ingenious ring retractor recently described by Hulsieck affords excellent exposure in hemorrhoidectomy and dispenses with the second assistant. One important factor in the mechanism of pain is pressure or tension on sensory nerves. In postoperative wounds, pressure on exposed sensory nerves is induced by increase in tissue tension resulting from edema, inflammation or reaction to tight sutures. To minimize postoperative pain, the operation of hemorrhoidectomy must be designed to eliminate increased tissue tension in the wound. The operation which best fulfils these criteria is a modification of the ligature or open operation first introduced in principle by Mr. Salmon at St. Mark's Hospital, London, over one hundred years ago. In this procedure the hemorrhoid is dissected cephalad, as described by Dr. Bacon. The hemorrhoidal mass containing only varicose veins, redundant rectal mucosa and skin is transfixed and tightly tied above the area of pain sensitivity (the anorectal line). The hemorrhoidal mass is amputated distal to the strangulating ligature, which sloughs off after nine days. The skin wound remains open for drainage, so avoiding tissue tension. Ten cc. of eucupine in oil is radially injected into the sphincter muscle. A thin sliver of petrolatum gauze remains in the wound. Postoperative urinary retention rarely occurs since I have been instilling 30 cc. of 0.5 per cent aqueous solution of mercurochrome into the bladder by catheter immediately after operation. Patients are immediately allowed a full smooth diet. Liquid petrolatum is administered every night. The pack is removed and the patient allowed out of bed after twenty-four hours. Sedation for pain is rarely necessary after the first twelve hours. Eucupine (iso-amyldihydrocupreine) is released slowly from its oil solution to the tissues, but its antispasmodic effect persists for from ten to fourteen days.

DR. HENRY RAILE, Salt Lake City: I am convinced that the muscle-avoiding technic outlined by Dr. Bacon is a desirable first step for avoiding postoperative pain following hemorrhoidectomy. The fact that the postoperative pain is frequently marked in so common an operation has put fear and dread into the minds of many in need of such attention. I have found that by following a simple postoperative procedure pain is not usually a fear-some necessity. A postoperative congestion in the operative field can be avoided by elevating the buttocks by placing the patient on his abdomen lying across two pillows immediately on his being placed in bed following the hemorrhoidectomy. Spasm of the anal sphincter and its accompanying pain can be avoided by applying at once hot hamamelis water packs for the first four hours, repeating the procedure daily for any beginning spasm. Analgesic oil injected into the anal sphincter muscles is also beneficial. Infection in the area of operation, another too frequent cause of postoperative pain, can usually be avoided by keeping the area scrupulously clean. Follow every defecation with a careful irrigation of warm physiologic solution of sodium chloride or boric acid solution and paint with some antiseptic preparation as merthiolate, metapen or mercurochrome. An early stool, usually on the second postoperative day, and the maintenance of a soft state of daily stools will aid in avoiding the occasional hard impacted stool, a near catastrophe for the patient.

DR. MALCOLM R. HILL, Los Angeles: The patient's ever present fear and dread of pain which follows anorectal surgery accounts for the frequent neglect of relatively simple problems. The medical profession has taken this problem altogether too lightly and considered it an incompatibility that in due time will correct itself after routine surgical measures are carried out. The author's paper emphasizes fundamental principles of great

importance. Any measure which can be instituted for the immediate relief of postoperative pain following rectal surgery is a worthy consideration. In Dr. Bacon's method it is hoped that in the hands of others it will prove an equally good panacea for the relief of pain. I myself have used several of the oil soluble anesthetic preparations obtainable through the drug trade. The results have not been too uniform. The first consideration in which I differ with Dr. Bacon is in the shaving of the perianal tissues preoperatively. This I believe produces in many cases a folliculitis to be followed by considerable annoyance from the outgrowing hair. Clipping of the hair certainly is adequate. In the second consideration I can see no logical reasoning to the weight-dosage ratio in spinal anesthesia for anorectal surgery. I find 50 mg. of procaine hydrochloride sufficient in the average hemorrhoid case irrespective of weight. I am willing to agree that suturing of perianal tissues in Dr. Bacon's hands is certain to be a success and probably a valuable aid in healing of the parts. However, to advocate the wide dissemination of this method of dealing with perianal tissues certainly will lead to many unsatisfactory results, perianal abscesses, prolonged annoyance and discomfort.

DR. LOUIS J. HIRSCHMAN, Detroit: The preparation of patients is important and so are many of the things used for postoperative relief, but I should like to say a word or two about operative procedures as mentioned by Dr. Bacon. He has correctly stated that the principal cause of postoperative pain in rectal surgery is the contraction of the sphincter muscle. That is very important. We must remember not to divulge the sphincter, particularly when the division is merely a tug of war between the operator and the patient. If the patient is under general anesthesia the operator wins out, but does it at the expense of a torn and overstretched, ecchymosed sphincter. Then the contractions of the sphincter do cause a great deal of pain. Another thing which insults the rectum is the use of postoperative packing. Many surgeons still pack the rectum full of rubber and gauze, and anything else that is handy, and then forget that a peristaltic stimulation is caused by a filled rectum, whether it is by stool or by gauze, and the peristaltic effort to expel this will cause a great deal of pain. I wish to differ with Dr. Bacon in one important matter. Remember that one of the most sensitive organs of the body is the skin. Every stitch we put into it traumatizes it just so much more. Whether one uses wire, silk or linen, every unnecessary needle hole causes unnecessary trauma to the skin and produces postoperative pain. So does the indiscriminate use of so many unnecessary instruments on the skin edges. One should remove rectal lesions with as small an incision as possible and use the sphincter as a purse string. The incisions pull together nicely without suture and one avoids the evulsive, ineffective malalignment. No matter how careful one is during the operation, mucus and bacteria will soil from the wound above, and it is easy for the surgeon to enclose these under his suture line. And as far as the question of postoperative anesthetic solutions are concerned, one must prepare the point of puncture not through the skin but through the raw surface by applying phenol before injecting, so as not to carry infective substances in with the needle. It is not so much the question of preventing postoperative pain as keeping the patient comfortable. Regardless of what else one uses, if the patient needs morphine, give it to him. Keep him comfortable always and the patient won't complain about pain following anorectal surgery.

DR. ARTHUR S. CALMAN, New York: I agree with Dr. Bacon that the foremost consideration in the operation of hemorrhoidectomy is the elimination of pain. But there are other even more important complications which must be avoided, such as injury to the fibers of the external sphincter by overstretching, as was emphasized by Dr. Hirschman. Postoperative hemorrhage and postoperative anorectal stricture must also be prevented. These complications are all due to the employment of the older methods of hemorrhoidectomy, such as the clamp and cautery and the excision with suture methods. I wish to call attention to an operation that I have devised and described recently under the title of submucous hemorrhoidectomy, which eliminates completely all the complications enumerated. I use a 1 per cent solution of procaine hydrochloride locally or a general anesthetic if the patient so desires. I don't stretch the

anal sphincter. The assistant brings the operative field in view by gentle manual retraction. I make a small transverse incision at the mucocutaneous junction and undermine the mucosa with a curved Mayo scissors, raising a flap, as in a cystocele operation, along the entire length of the hemorrhoid. A longitudinal incision is made along the midline of the mobilized mucosal flap, exposing the underlying hemorrhoid in its entirety. A suture ligature of number 00 plain catgut, which is absorbed shortly, is then passed around the distal end of the hemorrhoid and ligated. These flaps act like autografts. They agglutinate promptly to the underlying raw surface, thus avoiding scar and stricture formation during the healing process. No secondary hemorrhage can follow this operation, for there are no open granulating areas which could possibly become infected. In dealing with the combined external and internal hemorrhoid I begin with a V shaped incision at the base of the external hemorrhoid instead of a transverse incision at the mucocutaneous line and then proceed as described. I don't have to use more than a quarter of a grain of morphine as soon as the patient recovers from the anesthesia. A tablespoon of liquid petrolatum twice daily will give the patient a painless evacuation, there being no raw area exposed to irritation.

DR. HARRY E. BACON, Philadelphia: I should like to mention the fact that every effort is made to have the patient as comfortable as is possible. I do not spare morphine if it is necessary. I cannot agree with Dr. Granet as to the use of oil-soluble anesthetics. The work is far from completion but I have been able to show histologically that the process of healing is retarded. I believe that Dr. Malcolm Hill misunderstood me, because I do not give the patient morphine immediately after operation. That is done only when it is necessary.

## STUDIES OF THE PRINCIPLE IN LIVER EFFECTIVE IN PER- NICIOUS ANEMIA

### VI. RECENT ADVANCES IN THE PURIFICATION OF ACTIVE SUBSTANCES

BERNARD M. JACOBSON, M.D.

AND

YELLAPRAGADA SUBBAROW, PH.D., M.B.

BOSTON

It is now fourteen years since the original announcement by Minot and Murphy<sup>1</sup> of the effectiveness of liver therapy in pernicious anemia. During this period several groups of workers have attacked the problem of the isolation of the hemopoietically active material. It is fair to say that up to the present no such chemically pure and therapeutically active material has yet been isolated.<sup>2</sup> On the other hand, numerous advances toward this goal have been made, and it is our intent in this communication to summarize the present state of progress.

The history of the isolation from natural sources of biologically active materials, in all probability, reveals no instance replete with the difficulties attending the isolation of the antianemic principle of liver. This unique character of the liver principle is mainly consequent on the fact that for all other biologically active materials there exist satisfactory methods for the assay

This study has been supported by grants from the John and Mary R. Markle Foundation and from Dr. Clarence J. Gamble.

All the liver extract used in this investigation was prepared from material furnished by Lederle Laboratories, Inc., Pearl River, N. Y.

From the Medical Clinic, Massachusetts General Hospital, and the Departments of Medicine and Biological Chemistry, Harvard Medical School.

Read before the Section on Pharmacology and Therapeutics at the Ninety-First Annual Session of the American Medical Association, New York, June 12, 1940.

1. Minot, C. R., and Murphy, W. P.: The Treatment of Pernicious Anemia by a Special Diet, *J. A. M. A.* 87: 470-476 (Aug. 14) 1926.

2. Subbarow, Yellapragada; Hastings, A. B., and Elkin, M.: Chemistry of Anti-Pernicious Anemia Substances in Liver, *Ergebn. d. Vitamin-u. Hormonforsch.*, to be published.

of activity in animals, either in the normal state or in an induced pathologic state. The liver principle, on the other hand, in the light of present knowledge, evidences its biologic activity only by its therapeutic effects in pernicious anemia. Despite numerous attempts to find among animals a natural or induced condition in which the entire therapeutic activity of liver might be quantitated, no such proposed test has proved feasible. The guinea pig assay method<sup>3</sup> used by us has yielded valuable information concerning parts of the liver principle but cannot serve as an indicator of the entire therapeutic potency of liver. Thus the fractionation of crude liver into its component parts must depend on the assay of each fraction in patients suffering from a relapse of pernicious anemia. The attendant difficulties of this method of assay need no further amplification.

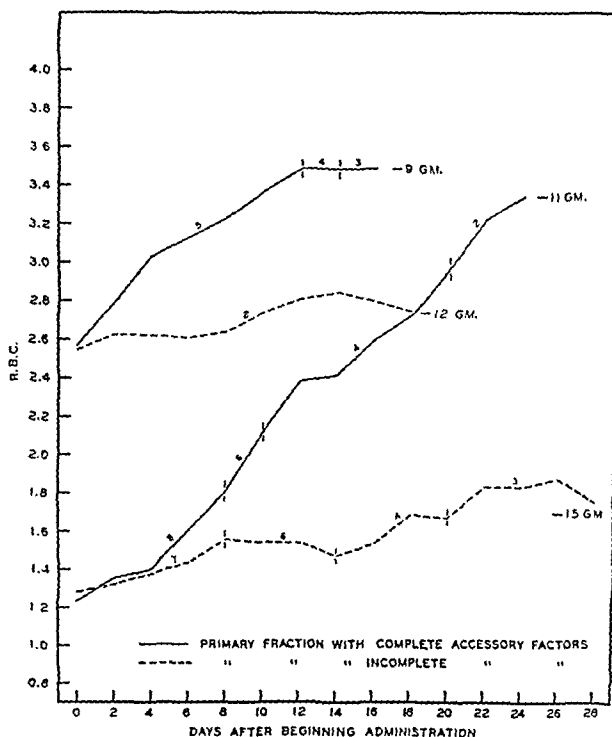


Chart 1.—Averages of erythrocyte regeneration curves following the administration of primary factor with incomplete and with complete complement of accessory factors. The number of patients studied in each period is shown by the small figures above each curve. The quantity at the end of each curve denotes the calculated average daily amount of primary factor administered, expressed in terms of amount of fresh liver from which the extract was derived.

Furthermore, an additional obstacle in the isolation of the liver principle is the apparent loss of therapeutic activity, as the fractionation proceeds, even in the absence of destructive physical or chemical procedures. This apparent loss, which we ascribe to the multiple nature of the liver principle, is discussed more fully later.

#### THE GROUNDWORK OF THE PROBLEM

The pioneer work of Cohn, Minot and their collaborators, extending from 1927 to 1930, furnished the basic method of the preliminary attack on whole liver, a starting point of virtually all later workers. Their attack consisted in the removal of the bulk of the liver proteins by means of heat coagulation on the acid side,

followed by the removal of additional protein material by means of 70 per cent alcohol, and finally by the precipitation of the greater part of the hemopoietically active substances in the presence of 95 per cent alcohol. This precipitate, the well known fraction G of Cohn,<sup>4</sup> was originally tested in patients with pernicious anemia by means of oral administration and, in doses of approximately 10 Gm. daily, was therapeutically effective.

By 1929, further purification of fraction G, in the hands of Cohn and his collaborators,<sup>5</sup> with the elimination of protein and of depressor constituents, resulted in a product that could be safely injected intravenously. This can be called a notable advance, for by this step there were eliminated the uncertainties of absorption following oral administration and the necessity of dealing with considerably larger quantities of material during the process of fractionation. All subsequent investigators have assayed their materials by means of parenteral administration either intravenously or, more commonly, intramuscularly.

By 1930 Cohn, McMeekin and Minot,<sup>6</sup> utilizing a variety of procedures, obtained a material which, in an injected dose of 140 mg., increased the concentration of erythrocytes of a patient with pernicious anemia by nearly 1,000,000 per cubic millimeter during the following ten days. This most highly purified material, in an amorphous state, had many of the properties of a nitrogenous base.

#### PARALLEL TRENDS OF INVESTIGATION

During the five years subsequent to the last communication in 1930 by Cohn,<sup>6</sup> three groups of workers were engaged in the isolation of the liver principle, each utilizing different methods of preparation and each contributing significantly to the process of purification. During the years 1935 and 1936 Dakin and West in New York, Subbarow and Jacobson in Boston and Laland and Klem in Oslo, Norway, published the results of their investigations.

Two important steps in purification were introduced by Dakin and West. In 1935 they<sup>7</sup> described the fact that therapeutically active material could be precipitated from Cohn's fraction G by Reinecke acid, and in 1936 Dakin, Ungley and West<sup>8</sup> showed that from the same source the active material could be brought down by saturated ammonium sulfate. The utilization of each of these procedures, followed by other steps, finally yielded their most highly purified fraction, which exhibited many of the properties of a peptide and which, in doses of from 40 to 100 mg., parenterally administered, was followed in most instances by moderately active therapeutic responses. Similar material in the form of the commercial preparation anahaemin was administered by Ungley, Davidson and Wayne<sup>9</sup> in doses of from 100 to 150 mg. during the first ten days, with resultant moderately active responses.

4. Cohn, E. J.; Minot, G. R.; Fulton, J. E.; Ulrichs, H. F.; Sargent, F. C.; Wear, J. H., and Murphy, W. P.: The Nature of the Material in Liver Effective in Pernicious Anemia, *J. Biol. Chem.* 74: 69-72 (July) 1927.

5. Cohn, E. J.; McMeekin, T. L., and Minot, G. R.: The Nature of the Material Effective in Pernicious Anemia, *Am. J. Physiol.* 90: 316-317 (Oct.) 1929.

6. Cohn, E. J.; McMeekin, T. L., and Minot, G. R.: The Nature of the Substance Effective in Pernicious Anemia, *Tr. A. Am. Physicians* 45: 343, 1930.

7. Dakin, H. D., and West, Randolph: Observations on the Chemical Nature of a Hematopoietic Substance Occurring in Liver, *J. Biol. Chem.* 109: 489-522 (May) 1935.

8. Dakin, H. D.; Ungley, C. C., and West, Randolph: Further Observations on the Chemical Nature of a Hematopoietic Substance Occurring in Liver, *J. Biol. Chem.* 115: 771-791 (Oct.) 1936.

9. Ungley, C. C.; Davidson, L. S. P., and Wayne, E. J.: The Treatment of Pernicious Anemia with Dakin and West's Liver Fraction, *Lancet* 1: 349-354 (Feb. 15) 1936.

3. Jacobson, B. M.: The Response of Guinea Pig's Reticulocytes to Substances Effective in Pernicious Anemia: A Biologic Assay of Therapeutic Potency of Liver Extracts, *J. Clin. Investigation* 14: 663-677 (Sept.) 1935.

In 1935 a novel and valuable step was arrived at by three groups of investigators independently of one another. Laland and Klem<sup>10</sup> working with Strandell,<sup>11</sup> Subbarow, Jacobson and Fiske<sup>12</sup> and Kyer<sup>13</sup> found that charcoal quantitatively adsorbs the active liver principle. The Scandinavian workers,<sup>14</sup> furthermore, observed that the active material could be eluted from the charcoal by means of phenol. With these two steps they arrived at considerable purification, with, however, apparent losses in potency. Thus several fractions (VIII, E and BF) reported by Strandell,<sup>11</sup> in average

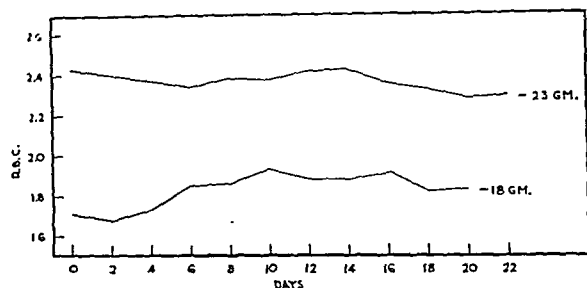


Chart 2.—Average erythrocyte regeneration curves following the administration of five accessory factors (tyrosine, complex purine, peptide, tryptophan, guanosine) without primary factor. The quantity at the end of each curve denotes the calculated average daily amount, in terms of whole liver from which the material was derived, of the fractions administered.

doses of 170 and 54 mg., respectively, during periods of from four to five weeks, showed moderate hemopoietic activity, while a much more highly purified fraction, in an average total dose of 5 mg. during a period of five weeks, showed significantly less activity.

Both the innovations of Dakin and West and of Laland and Klem were utilized in 1936 by Ungley,<sup>15</sup> who treated anahaemin with phenol, followed by methyl alcohol precipitation of active material from the phenolic solution. This precipitate, in average doses of from 34 to 75 mg. per ten days, exhibited moderate therapeutic activity, no greater, however, than similar doses of less purified material used by Dakin, Ungley and West.<sup>6</sup>

In contrast to the Scandinavian workers, both Subbarow, Jacobson and Fiske<sup>16</sup> and Kyer<sup>13</sup> used charcoal for adsorption, followed by alcoholic elution of active material. This method has proved highly successful, always yielding chemically crude extracts maximally active in doses of approximately 140 mg. per ten days, an amount of extract derived from 100 Gm. of whole liver.

Finally from Switzerland there have appeared, in the last three years, reports of further attempts to isolate the liver principle. Karrer, Frei and Fritzsche<sup>17</sup> and

Karrer, Frei and Ringier<sup>18</sup> have reported briefly on some properties of highly purified materials, with no description, however, of the method of preparation. Their best material they reported to be active in doses of from 8 to 10 mg.<sup>18</sup> In 1938 Koller<sup>19</sup> presented in detail the assays of preparations furnished him by Karrer. In contrast to the statement by the latter, Koller's data concerning the three most highly purified fractions (extracts 25, 28, 35) administered in initial doses of 20, 15 and 20 mg., respectively, indicated only slight therapeutic activity. After the administration of cruder fractions, however, in an average dose of 19 mg. per ten days, the resultant responses demonstrated moderate activity (chart 4).

#### DIVERGENT TRENDS OF INVESTIGATION

It is evident that the accomplishments of the several groups of workers just described have in common a position far short of the goal of the isolation of the liver principle. It is axiomatic that the fulfilment of the quest must be the isolation in pure chemical form of the principle that completely duplicates the therapeutic activity of whole liver. If it is assumed that the liver principle consists of a unitary chemical compound, then it is fair to describe these advances as extremely divergent.

Divergence of trends of investigation had its beginning in the contrasts between the chemical properties described for their purest material by Cohn, McMeekin and Minot in 1930<sup>6</sup> and those reported by Dakin and West in 1935,<sup>7</sup> and again in 1936 by Dakin, Ungley and West.<sup>8</sup> But in 1935 Fiske, Subbarow and Jacobson<sup>20</sup> branched off on a new path with their hypothesis

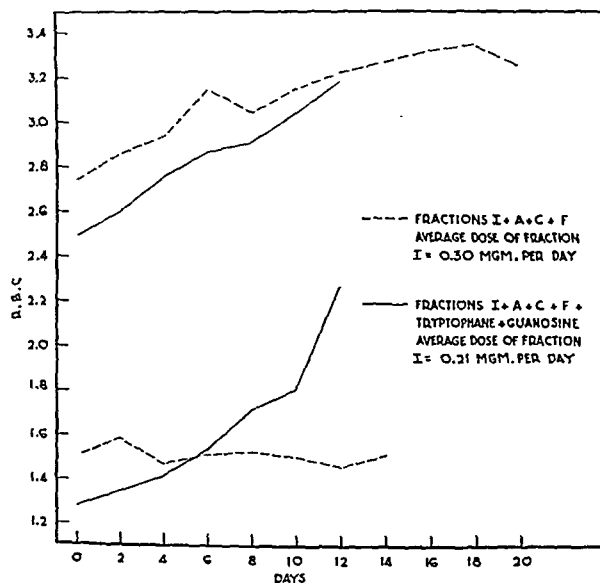


Chart 3.—Average erythrocyte regeneration curves following the administration of purified primary factor (fraction I) with three accessory factors and with five accessory factors.

of the multiple nature of the liver principle. The evidence for this view was further presented by Subbarow and Jacobson<sup>21</sup> in 1936 and more completely

10. Laland, Per, and Klem, Aage: Experiments to Isolate the Antianemic Principle of the Liver: Chemical Part, *Acta med. Scandinav.* 88: 620-623 (May 27) 1936.

11. Strandell, Birger: Experiments to Isolate the Antianemic Principle of the Liver: Clinical Part, *Acta med. Scandinav.*, 1935, supp. 71, pp. 1-52.

12. Subbarow, Yellapragada; Jacobson, B. M., and Fiske, C. H.: The Separation of the Substances in Liver Which Are Reticulocytogenic in the Guinea Pig and Which Are Therapeutically Effective in Experimental Canine Blacktongue, *New England J. Med.* 212: 663-664 (April 11) 1935.

13. Kyer, Jean L.: Charcoal Adsorption As a Method for the Preparation of Concentrated Liver Extract, *Proc. Soc. Exper. Biol. & Med.* 32: 1102-1103 (April) 1935.

14. Laland and Klem, "Strandell."

15. Ungley, C. C.: Further Purification of Dakin and West's Liver Fraction: Purified Anahaemin Compared with Original Product in Regard to Effect in Pernicious Anemia, *Lancet* 2: 1513-1518 (Dec. 26) 1936.

16. Subbarow, Yellapragada; Jacobson, B. M., and Fiske, C. H.: A Partially Purified Liver Extract Therapeutically Effective in Pernicious Anemia, *New England J. Med.* 214: 194 (Jan. 30) 1936; footnote 12.

17. Karrer, Paul; Frei, P., and Fritzsche, H.: Ueber einen Bestandteil von gegen Perniziöseanämie hoch aktiven Leberpräparaten, *Helvet. chim. acta* 20: 622, 1937.

18. Karrer, Paul; Frei, P., and Ringier, B. H.: Bestandteile von gegen Perniziöseanämie hoch aktiven Leberpräparaten, *Helvet. chim. acta* 21: 314-315, 1938.

19. Koller, F.: Ueber die klinische Wirksamkeit hochkonzentrierter Leberextrakte, *Deutsches Arch. f. klin. Med.* 183: 296-314, 1938.

20. Fiske, C. H.; Subbarow, Yellapragada, and Jacobson, B. M.: The Multiple Nature of the Pernicious Anemia Principle in Liver, *J. Clin. Investigation* 14: 709 (July) 1935.

21. Subbarow, Yellapragada, and Jacobson, B. M.: Chemical Studies of the Pernicious Anemia Principle in Liver, *J. Biol. Chem.* 114: cii-ciii (May) 1936.

amplified in 1937.<sup>22</sup> Early in the course of our work certain observations suggested the possibility that the therapeutic activity of liver extract might depend on the presence of several distinct substances.<sup>20</sup> The observations comprised a body of indirect evidence that need not concern us at present. The direct evidence for the multiple factor hypothesis was the fact that continued purification of crude liver extract, in the absence of significant losses and of destructive procedures, resulted in partial or complete extinction of therapeutic activity. But the admixture with such purified materials of other fractions derived from liver resulted in the recovery of therapeutic activity.<sup>22</sup> The latter fractions have been termed accessory factors, for, while by themselves therapeutically inert, they appeared to augment the activity of the primary factor (or factors) contained in the purified fractions.<sup>22</sup>

Up to 1938 there were isolated from crude liver extract three distinct materials considered to act as accessory factors. These were *l*-tyrosine (fraction A)<sup>12</sup> in a yield of 6 mg. from 100 Gm. of whole liver, a complex purine (fraction C)<sup>12</sup> in a yield of 11 mg., and a peptide (fraction F)<sup>21</sup> in a yield of 14 mg.

In 1938 Sladek and Kyer<sup>23</sup> described the preparation of an alcoholic elute of charcoal adsorption with properties very similar to such an elute described by us in 1936.<sup>10</sup> Sladek and Kyer state that they discard the complex purine which separates out after concentration of the elute, since "the concentrate from which it is filtered has shown satisfactory hematopoietic activity." Well it might, for this filtrate, as noted diagrammatically by us,<sup>22</sup> still contains a significant amount of the purine. Furthermore, Sladek and Kyer describe the presence of tyrosine in their charcoal adsorbate and refer to us<sup>12</sup> as stating that the tyrosine is to be found in the charcoal filtrate. On the contrary, although "the solution was decolorized with a small amount of charcoal,"<sup>12</sup> this amount is insufficient to adsorb any significant quantity of tyrosine. Norit charcoal,<sup>16</sup> when used in an adequate amount, has always quantitatively adsorbed the tyrosine present in crude commercial liver extract.

The resemblance of this purine to the type of compound known as pterine, of which an example is xanthopterin, the pigment of the wings of yellow butterflies, was pointed out in 1935.<sup>12</sup> It is of interest that in a search for the factor in liver curative of goat's milk anemia in rats, Tschesche and Wolf<sup>24</sup> obtained high concentrations of the factor in purine fractions of liver extract and also in similar fractions of human urine. In view of the isolation by Koscharka<sup>25</sup> from urine of a pterine, designated by him uropterine, probably identical with xanthopterin from butterflies' wings, Tschesche and Wolf assayed both materials in pure form of their activity in goat's milk anemia and found them strongly curative in doses as small as 0.5 microgram a day. A similar activity was shown by a substance prepared from liver and identical with the complex purine of ours.

Crude sources of primary factor were obtained by us by means of alcohol-ether precipitation on the previously described alcoholic elute of charcoal adsorption.<sup>26</sup> Such sources of primary factor were described as fraction H, derived from a fuller's earth filtrate on the alcoholic elute and obtained in a yield of 20 mg. from

100 Gm. of whole liver,<sup>22</sup> and fraction E, derived directly from the alcoholic elute, in a similar yield of 20 mg.<sup>22</sup> These two materials differed from each other only in the fact that fraction E contained minimal amounts of the accessory factors while fraction H was almost entirely devoid of these substances. It was first demonstrated in eleven experimental periods among 9 patients with pernicious anemia that the accessory factors, singly or in combination, were entirely inert.<sup>22</sup> Then, in nine experiments it was shown that the sources of primary factor, either alone or when administered together with any two of the three accessory factors, exerted either no hemopoietic effect whatever or an ill sustained, slight effect.<sup>22</sup> Finally, the combination of all three accessory factors with either of the sources of primary factor, in thirteen experiments, induced responses indicating moderate therapeutic activity. In chart 1 are reproduced from a previous publication<sup>22</sup> averages of such erythrocyte regeneration curves, demonstrating in a clear-cut fashion the augmentative action of the accessory factors on that of the primary factor. In chart 4 it is evident that the particular dosage administered of this combination of factors approximates, but does not equal, the effect induced by an amount of commercial liver extract<sup>27</sup> derived from a similar quantity of whole liver (compare the Jacobson and Subbarow 1937 curve with the Murphy-Hartfall curve).

It should be emphasized that this augmentative action of the accessory factors does not depend on additive effects of a substance common to all, for the accessory factors, in the absence of primary factor, were administered in large dosage, with no resultant response whatever.<sup>22</sup>

It was pointed out in 1937<sup>22</sup> that all possible accessory factors in crude liver extract might not be represented by only tyrosine, the complex purine and the peptide. In 1938 Subbarow, Jacobson and Hartfall<sup>28</sup> isolated from fraction H two substances in a pure state and identified them as tryptophan and guanosine respectively. The former was obtained in a yield of 8 mg. and the latter in a yield of 5 mg., respectively, from 100 Gm. of whole liver. Certain indirect evidence suggested the possibility that these substances might act as additional accessory factors. In the absence of primary factor they too exert no therapeutic effect, even in the presence of the other three accessory factors. In chart 2 are depicted the results of the administration of large amounts of each of the five substances together in twelve experiments among eleven different patients with pernicious anemia. The average curves of erythrocyte regeneration over a period of twenty days included all cases, but in eight cases the periods of observation were considerably longer, ranging from thirty-seven to forty-four days. These data amplify the previously reported results after the administration of only fractions A, C and F<sup>22</sup> and demonstrate clearly that the five accessory factors together, in the absence of primary factor, are completely devoid of therapeutic action.

Finally, the additional augmentative effect exerted by tryptophan and guanosine together is indicated by the data in chart 3.<sup>29</sup> In these experiments the source of the primary factor was a more highly purified material.

22. Jacobson, B. M., and Subbarow, Yellapragada: Studies of the Principle in Liver Effective in Pernicious Anemia: IV. The Therapeutic Activity of Its Multiple Factors, *J. Clin. Investigation* 16: 573-585 (July) 1937.

23. Sladek, Jaromil, and Kyer, Jean: Preparation and Properties of the Charcoal Adsorbate of Liver Extract, *Proc. Soc. Exper. Biol. & Med.* 29: 227-230 (Nov.) 1938.

24. Tschesche, R., and Wolf, H. J.: Ueber den Ziegenmilchanämiefaktor von Rominger und Bomskov, *Ztschr. f. physiol. Chem.* 244: 1-3, 1936; Die Wirkung der Pterine und einiger anderer Stoffe auf den Blutbild distänämischer Jungtiere und ausgewachsener Ratten, *ibid.* 248: 34-40, 1937.

25. Koscharka, W.: Isolierung eines gelben Farbstoffes (Uropterin) aus Menschenharn, *Ztschr. f. physiol. Chem.* 240: 127-151, 1936.

26. Subbarow, Yellapragada; Jacobson, B. M., and Prochownik, V.: Studies of the Pernicious Anemia Principle in Liver: III. The Isolation and Properties of a Substance with Primary Therapeutic Activity, *J. Am. Chem. Soc.* 58: 2234-2236, 1936.

27. One cc. Concentrated Solution Liver Extract Parenteral-Lederle, N. N. R.

28. Subbarow, Yellapragada; Jacobson, B. M., and Hartfall, S. J.: Studies of the Principle in Liver Effective in Pernicious Anemia: V. Additional Accessory Factors and Further Properties of the Primary Factor, *J. Clin. Investigation* 17: 517 (July) 1938.

29. Dr. George V. LeRoy of the University of Chicago carried out the assay of these materials in one patient.



fraction I,<sup>26</sup> and was administered with fractions A, C and F to 8 patients and together with all five accessory factors to 8 other patients. The amounts of primary factor administered in both series of experiments were small (0.30 mg. a day, and 0.21 mg. a day, respectively) in order to render more apparent any additional augmentative action of tryptophan and guanosine. Such an action seems to be indicated by the contrasting rates of erythrocyte production, but only at initial erythrocyte levels less than 2 million per cubic millimeter. Is it possible that this difference between the responses of patients at widely different erythrocyte levels indicates more of a deficiency of the latter two substances in patients at the lower level? At present we possess no further data bearing on this interesting possibility.

The results suggesting the additional augmentative effect exerted by tryptophan and guanosine are the basis for our use, during the past three years, of all five factors in the assay of various materials for their activity as primary factor. In other words, the accessory factors, usually administered in doses of material derived from 10 to 20 Gm. of whole liver a day (4.4 to 8.8 mg. of solids), have been maintained constant, while the only variable in our assays has been the nature and the amount administered of various fractions containing primary factor.

#### A POSSIBLE UNIFICATION OF DIVERGENT TRENDS

Our multiple factor hypothesis<sup>22</sup> is not shared by the other workers in the field. On the other hand, so long as the liver principle remains in the present impure, noncrystalline state, in the hands of all investigators, every therapeutically active preparation is a mixture of several different substances. This fact is borne out by the extreme variation of the amounts of preparations of different workers that are required to evoke similar therapeutic responses, a degree of variation not attributable to such biologically active pure substances as thiamine, riboflavin, nicotinic acid or ascorbic acid. A consideration of these different therapeutic responses in pernicious anemia may explain some of the discrepancies.

It has long been our belief that preparations derived from liver, when administered in adequate dosage, can be termed active only when they duplicate the action of crude liver extract; that is, when they induce the usual clinical response that is always accompanied by a satisfactory rate of regeneration of erythrocytes. The quantitative measure of therapeutic activity on which we place most emphasis is the rate of erythrocyte regeneration rather than the height of the reticulocyte response. Although the reticulocyte response alone, early in the course of an assay, may indicate qualitatively the presence of active material, and under certain conditions may aid in the evaluation of the comparative potency of two different materials,<sup>30</sup> it can hardly serve as a quantitative measure of the therapeutic activity induced by liver extract. Schipdt<sup>31</sup> has recently clearly demonstrated in a number of cases at different initial erythrocyte levels, cases under treatment with similar amounts of a commercial liver extract, that the height of the reticulocyte peak is related to the initial erythrocyte level rather than to the rate of regeneration of erythrocytes.

How long a period of observation of the rate of rise of erythrocytes is adequate for correct evaluation of a preparation? Although ideally the material to be assayed might be administered until the patient has attained a complete remission and normal level of erythrocytes and of hemoglobin, such a prolonged period of assay is rarely feasible, and we have usually attempted to construct an erythrocyte regeneration curve over a period of at least twenty days.<sup>32</sup> By statistical methods, Schipdt<sup>31</sup> has determined that the rate of rise of erythrocytes during the initial period of twenty days can serve as a valid indicator of the slope of the complete curve of erythrocyte production.

In chart 4 is presented a comparison of the erythrocytogenic activities of various preparations already discussed. Each curve has been constructed from the data contained in the publications of the several authors and represents the average of the responses of a number of patients, almost all at initial erythrocyte levels between 1.00 and 1.99 million per cubic millimeter. The dosage of materials administered has been calculated in terms

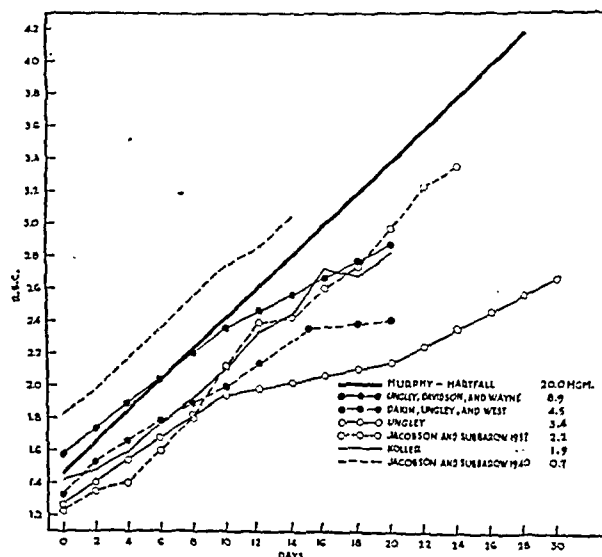


Chart 4.—Average erythrocyte regeneration curves following the administration of various purified liver extracts. The calculated average daily amount of material administered is recorded in the legend. The sources of these data are contained in the text. (The daily doses recorded for the curves of Jacobson and Subbarow refer only to the amount of primary factor administered; in addition, three accessory factors were administered in the 1937 curve, in a daily amount of 3.4 mg. and five accessory factors were administered in the 1940 curve in a daily amount of 6.2 mg.)

of the amount administered per day and is appended to chart 4. Finally, in order to facilitate comparison with a maximal rate of erythrocyte regeneration there has been depicted the rise induced by a moderate dosage of commercial liver extract.<sup>33</sup> This curve has been constructed from combined data taken from the protocols of Murphy<sup>34</sup> and of Hartfall.<sup>35</sup>

From chart 4 it is evident that the hemopoietic activity of each of the purified materials falls short of that of the crude commercial liver extract but that this rate of erythrocyte regeneration is most closely approximated by our 1940 curve induced by material to be described

30. Minet, G. R., and Castle, W. B.: The Interpretation of Reticulocyte Reactions: Their Value in Determining the Potency of Therapeutic Materials, Especially in Pernicious Anemia, *Lancet* 2: 319-330 (Aug. 10) 1935.

31. Schipdt, E.: Observations on Blood Regeneration in Man: IV. The Rise in Red Blood Cells in Pernicious Anemia After Specific Treatment: Attempt to Institute a Standard for Valuation of Treatment, *Acta med. Scandinav.* 98: 449-467, 1939.

32. The methods used in such an assay have been described previously.<sup>22</sup>

33. One cc. Concentrated Solution Liver Extract Parenteral-Lederle, N. N. R., administered in an average daily dose of 0.14 cc., containing 20 mg. of solids, derived from 14 Gm. of whole liver.

34. Murphy, W. P.: Treatment of Pernicious Anemia with Intramuscular Injections of a Highly Concentrated Solution of Liver Extract, *Am. J. M. Sc.* 191: 597-607 (May) 1936.

35. Hartfall, S. J.: Experiences with a Concentrated Whole Liver Extract, *Lancet* 2: 317-321 (Aug. 7) 1937.

and administered as primary factor in an average dose of 0.7 mg. a day (together with the five accessory factors in an average total dose of 6.2 mg. a day). Less satisfactory, but nevertheless indicative of good activity, are the three curves of Ungley, Davidson and Wayne, of Koller and of Jacobson and Subbarow, 1937. Definitely less activity is indicated by the curves of Dakin, Ungley and West and of Ungley.

In chart 4 it is to be noted that the curves of Ungley, Davidson and Wayne and of Dakin, Ungley and West, based on the administration of similar material<sup>9</sup> in daily doses of 8.9 and 4.5 mg. respectively, differ significantly from one another, and even the larger dose does not induce the maximal response. This may mean that a major portion of Dakin, Ungley and West's preparation consists of inert material with a relatively small content of active substances or, on the basis of the multiple factor theory, that the preparation contains a relatively small amount either of primary factor or of all accessory factors. A similar interpretation can be given to the material administered by Ungley. Koller's curve, based on a dose of only 1.9 mg. a day, indicates good activity, but this rate of erythrocyte regeneration is nevertheless

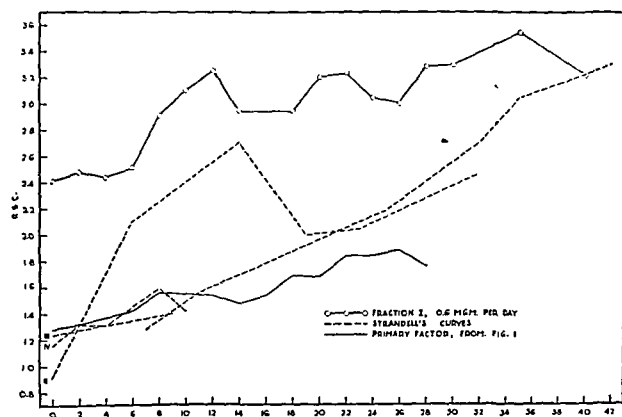


Chart 5.—Erythrocyte regeneration curves following the administration of primary factor.

slower than that of Jacobson and Subbarow, 1940, following the administration of only 0.7 mg. a day in addition to accessory factors. That the material represented by Koller's curve (material furnished by Karrer and his associates,<sup>36</sup> despite its activity in relatively small dosage, consists of more than one substance is implied by Koller,<sup>19</sup> who states that his fractions numbered 25, 28 and 35 are the most highly purified, containing no traces of phosphorus or pentose. None of these fractions are represented in Koller's curve depicted in chart 4. It is of interest, in connection with the multiple factor theory, to note the responses reported by Koller to the administration of these most highly purified fractions. Thus, after the administration of 20 mg. of fraction 25 the erythrocytes rose in twenty days from 3.0 to 3.4 million; in a case under treatment with 15 mg. of fraction 28, the erythrocytes numbered 2.6 million initially and after twelve days 2.5 million; and following the administration of 18 mg. of fraction 35 the erythrocytes rose in six days from 1.4 to 1.8 million. Excluding the latter case, which was observed for an insufficiently long period, it is evident that in the cases tested by Koller the purest preparations of Karrer and his associates were therapeutically virtually inert. It appears likely, therefore, that the

limiting factor in Karrer's preparations is the absence of an optimal amount of accessory substances.

Mention is made later in this paper of the most highly purified material described by Laland and Klem<sup>37</sup> obtained in a yield of 0.35 mg. from 100 Gm. of whole liver. Laland and Klem state that a good antianemic effect was observed by Strandell and his collaborators<sup>37</sup> after the injection of only 0.7 mg. This interpretation is not shared by us, for the data of Strandell furnish evidence of only slight to moderate therapeutic activity. The erythrocyte regeneration curves in the four cases under treatment by Strandell are portrayed in chart 5. Although each of these cases exhibited a moderate rise of reticulocytes, the erythrocyte production was moderately submaximal in case 1, markedly submaximal in case 2 and virtually absent in cases 3 and 4.

In chart 5, in addition to these four curves, there is reproduced the lower curve of chart 1, portraying the slight effect on erythrocytes of a moderate dosage of crude primary factor without adequate amounts of accessory factors, and also a curve of erythrocyte regeneration in a case previously reported (case 23<sup>38</sup>). In the latter case a large amount of relatively pure primary factor (fraction I) was administered in an average dose of 0.6 mg. a day, without accessory factors, over a period of forty days. It is evident that the initial rise of erythrocytes in this instance is limited to the first ten days and that thereafter no further change took place. Of the same order of magnitude are the slopes of Strandell's curves in chart 5. All these curves appear typical of the action of primary factor without accessory factors and certainly do not reproduce the action in pernicious anemia of crude liver extract.

It seems to us, therefore, that the variations in the results of the several groups of workers may depend in part on quantitatively and possibly also qualitatively differing complements of accessory factors contained in the preparations. That only the substances described by us as accessory factors may exert such an action is not established. That other substances present as contaminants in many preparations may act in this fashion is possible.

Finally, the multiple nature of the liver principle, as elaborated by us, has found numerous analogies in the advances in nutritional physiology during the last decade. This concept is well illustrated by the recent observations of Subbarow and Trager<sup>38</sup> that essential accessory growth factors required by mosquito larvae include, in addition to other factors, such chemically unrelated substances as thiamine, riboflavin, pantothenic acid and vitamin B<sub>6</sub>.

#### RECENT STUDIES OF THE CHEMICAL PROPERTIES OF THE LIVER PRINCIPLE

In the published reports of the most highly purified materials in recent years there have been described both concordant and discordant properties. In 1930 Cohn, McMeekin and Minot,<sup>6</sup> on the basis of the properties of their best material therapeutically active in an initial dose of 140 mg., concluded that "the very small amount of  $\alpha$ -amino nitrogen suggests that one is not dealing with an  $\alpha$ -amino acid but with an  $\omega$ -amino or imino-acid. The low nitrogen content appears to exclude purine or pyrimidine bases but not ring compounds of

37. Strandell, Birger; Poulsen, L., and Scharum-Hansen, H.: Experiments to Isolate the Antianemic Principle of the Liver: Clinical Part. Acta med. Scandinav. 88: 624-625 (May 27) 1936.

38. Subbarow, Yellapragada, and Trager, W.: The Chemical Nature of Growth Factors Required by Mosquito Larvae: II. Pantothenic Acid and Vitamin B<sub>6</sub>. J. Exper. Med. 23: 561-568 (May 20) 1940.

36. Karrer, Frei and Fritzsche.<sup>12</sup> Karrer, Frei and Ringier.<sup>13</sup>

pyrrole or pyridine types, though the purest fractions do not give the pine-splinter test characteristic of pyrroles." Opposed to this characterization is the conclusion reached in 1936 by Dakin, Ungley and West<sup>8</sup> on the basis of the properties of their best material, moderately active in an average dose of 45 mg. per ten days (chart 4), "that the hematopoietic substance in liver is, or is associated with, a peptide, possessing many but by no means all of the properties of an albumose."

This peptide may or may not be identical with the peptide obtained as a crystalline rhodanilate and reineckate in 1936 by us<sup>21</sup> and described as fraction F, an accessory factor.<sup>22</sup> In our hands this pure peptide, when administered without a source of primary factor in cases of pernicious anemia has been therapeutically inert, as previously described.

In 1939, Dakin and West<sup>30</sup> reported further evidence for the peptide nature of the substance described by them in 1936,<sup>8</sup> by virtue of the fact that it could be partially brought down by a variety of typical albumose precipitants, such as nucleic acid, bile and taurocholic acid, with satisfactory therapeutic activity induced in one case by 30 mg. of such material.

By means of a series of procedures taken from almost all previous workers in the field, Mazza and Penati<sup>40</sup> obtained highly purified material containing a pterine and a polypeptide in combination with adenine nucleotide. The significance of this material is obscured by the fact that it was derived from a cruder fraction (B), described by these authors as therapeutically active but which, on the basis of the data at hand, was virtually inert.

Differing considerably from these two descriptions are the properties described in 1936 by both Laland and Klem and by Subbarow, Jacobson and Prochownik. Laland and Klem<sup>10</sup> proceeded from their material described in 1935 by Strandell<sup>11</sup> by means of further charcoal adsorption, phenol elution and salting out with ammonium sulfate and finally obtained material in a yield of 0.35 mg. from 100 Gm. of whole liver. Subbarow and his collaborators<sup>29</sup> proceeded from their previously described ethyl alcohol elute<sup>16</sup> by means of the removal of inert material with fuller's earth, precipitation with Reinecke acid, following the procedure of Dakin and West,<sup>7</sup> regeneration of the Reinecke precipitate with amyl alcohol extraction, finally bringing down, with a mixture of acetone and ether, a preparation (fraction I) in a yield of 2 mg. from 100 Gm. of liver. The therapeutic activities of these two products have already been discussed, and it has been pointed out that each appears to act as a primary factor. Both of these materials exhibit a degree of concordance unparalleled in the literature, for the properties show similarities in elementary composition and in one point of inflection of the absorption spectrum in the ultraviolet.

Differing in properties from those of all the purified materials discussed are the preparations briefly described by Karrer, Frei and Fritzsche in 1937,<sup>17</sup> by Karrer, Frei and Ringier in 1938<sup>18</sup> and assayed by Koller in 1938.<sup>19</sup> These authors make no mention of the method of preparation. The therapeutic activity of their material has already been discussed.

In 1936, Wilkinson<sup>41</sup> reported the use of Reinecke acid in the purification of active material, with no description, however, of the method of preparation. The purest material was administered to three patients in doses of 18, 27 and 36 mg., respectively, with resultant initial responses indicative of moderate activity, but neither patient was observed long enough to permit a satisfactory evaluation of the therapeutic potency.

30. Dakin, H. D., and West, Randolph: A Hematopoietic Substance in Liver, *Proc. Soc. Exper. Biol. & Med.* **40**: 124-126 (Jan.) 1939.

40. Mazza, F. P., and Penati, F.: Sulla natura chimica del principio antipernicioso del fegato, *Arch. di sc. biol.* **23**: 443-471 (Oct.-Dec.) 1937; *Nota II*, *ibid.* *Arch. di sc. biol.* **24**: 83-88 (Feb.) 1938.

41. Wilkinson, J. F.: Note on the Antianemic Principle of Liver, *Lancet* **1**: 354-356 (Feb. 15) 1936.

In 1938 Subbarow, Jacobson and Hartfall<sup>28</sup> reported that a derivative of fraction I exhibited chemical properties suggestive of a complex pyridine compound. Further evidence for the pyridine ring as a part of the primary factor was furnished by the fact that moderate therapeutic responses in two cases were induced by the parenteral administration of synthetic nicotinic acid amide in a dosage of 1 and 2 mg. a day, respectively, together with three accessory factors (tyrosine, complex purine and peptide). Finally, during the past year and a half we have modified our method of preparation with resultant improvement in the yield of therapeutically active primary factor.<sup>42</sup> From the alcohol elute the primary factor has been precipitated out by means of Reinecke acid, the regenerated reineckate has been treated with charcoal and then, after the procedure of Laland and Klem,<sup>10</sup> the adsorbate has been eluted with phenol. Further treatment of the phenol elute with various organic precipitants has yielded amorphous materials in quantities of approximately 3 to 10 mg. of organic solids from 100 Gm. of whole liver, with excellent therapeutic activity as primary factor among four patients in an average dosage of 7 mg. per ten days (chart 4).

This, then, is the present known status of the liver principle. Both differences and similarities in methods of preparation and in properties of amorphous materials have been described by various workers during the past four years. Until the primary factor is obtained in crystalline form, this discordant state will exist. Although progress during the last decade has been discontinuous, the trend of investigation augurs the attainment of the goal in the not too distant future.

#### ABSTRACT OF DISCUSSION

DR. RANDOLPH WEST, New York: There are certain points that should be emphasized, and one is that the mixture of peptides described by Dakin and later independently by Karrer in Switzerland does not contain any of the accessory factors mentioned. The best preparations of the peptides give no bands in the ultraviolet, and the amino acids isolated from these peptides do not give any either. None of the ring acids are present, tyrosine is not present, no pterins are present, no purines are present, so, whatever the effect of these other substances, they are not the substances which have to do with the essential chemical lesion in pernicious anemia. They may accentuate the action of the essential substance in pernicious anemia, but it is important that attention be focused on the substance which actually has to do with the essential chemical lesion in pernicious anemia, and the best available work shows that this is a mixture of peptides by no means chemically pure, but certainly not containing any of the other substances. I think that in orienting future chemical work a careful analysis of the peptide mixtures by modern methods, the ultracentrifuge, dialysis, electrophoresis and other methods of that sort, are imperative, and I am quite sure that while the substances described are accurately described by Dr. Subbarow and Dr. Jacobson and may accentuate the effect of the essential materials missing in pernicious anemia, they in themselves have nothing directly to do with the chemical lesion in pernicious anemia. We must attack the center of the problem and not the periphery.

DR. BERNARD M. JACOBSON, Boston: We agree with Dr. West that we are focusing our attention on the factor in liver that does the trick in pernicious anemia or, in our terms, the primary factor. Whatever disagreement there may be between our group and other groups on the role of the accessory factors in completing the hemopoietic and clinical response to liver extract, we do not disagree on the necessity for the isolation

42. The details of the method of preparation will appear in a forthcoming publication.

in pure chemical form of the primary or principal liver factor. Up to the present, unfortunately, there still exists a good deal of disagreement between the properties of the factor reported by Klem in Oslo, by Dakin and West in New York, by Karrer in Zurich and by our group in Boston. On the other hand, as long as we are all dealing with admittedly amorphous materials these difficulties will continue to exist and will be abolished only after materials are obtained in pure crystalline state.

## CEREBRAL SPASTIC PARALYSIS

### THE OBSTETRIC HISTORY OF ONE HUNDRED AND EIGHTY-FIVE CASES

GERALD W. GUSTAFSON, M.D.

AND

GEORGE J. GARCEAU, M.D.

INDIANAPOLIS

This study of the obstetric history of 185 cases of cerebral spastic paralysis was undertaken without preconceived ideas as to the most important etiologic factors involved. Schreiber<sup>1</sup> expressed the belief that apnea is the biggest single factor in the production of cerebral injury. He stated that analgesic drugs, given in greater amounts than the pharmacologic dosage, may, in many instances, be the causative factor of fetal anoxemia with resultant cerebral damage in the infant. Cole and his associates<sup>2</sup> stated that prematurity is the most important factor in the etiology of neonatal asphyxia. Other well recognized factors are the normal forces of labor, oxytocics, operative intervention, nonintervention, postnatal infection and trauma in the baby. As the majority of cases of cerebral spastic palsy are associated with definite cerebral injury at birth, we thought it worth while to review the obstetric histories of a group of children with this disorder.

**Material.**—It seemed most logical to take advantage of the patients available in the cerebral spastic palsy clinic at the James Whitcomb Riley Hospital for Children of the Indiana University Medical Center. Therefore a history was taken from the mothers of 185 of these patients. Obviously, the amount of information and various details was not as complete as could be obtained by delving into thousands of hospital obstetric records to obtain a similar number of cases; nevertheless, the salient features of each case are present and we are dealing with known facts and not a hypothesis. We feel confident of the accuracy of the data here submitted. Twenty-three infants (12.4 per cent) were delivered in hospitals, while 162 (87.6 per cent) were delivered in homes. Analgesia and anesthesia played little if any part in this series. Of those delivered at home, an occasional injection of morphine and a small amount of ether were given, the majority of the mothers being awake at or shortly after delivery. In no case did there seem to be any relationship between analgesia or anesthesia and the etiology of the condition. This series, then, seems to constitute a cross section of American obstetric cases in which cerebral injury occurred in the infant though labors were conducted without or with a small amount of analgesia and anesthesia. In

only 1 child was there a positive Wassermann reaction. The mother of another was syphilitic but had been adequately treated, and her baby's Wassermann reaction was negative. There were 8 patients in whom the lesion appeared to be due to postnatal infection or trauma.

In 18 children no definite cause could be found. We hold the opinion that some of these lesions are probably developmental in nature. We realize the lack of evidence. Necropsy would be necessary to defend this opinion.

**Age and Parity of the Mothers.**—The age of the mothers is given in chart 1. The greatest number of cases, namely 60, or approximately 32 per cent, occurred in labors of women between the ages of 20 and 25, while only 7 children, or 3.7 per cent, had mothers between the ages of 40 and 45. The parity of the mothers is shown in the table. We would expect to find the largest number of injuries in infants of primiparas, and such is the case, as 106 of the injured infants were first born. After the third child the incidence of cerebral injury is much lower. Boys, because of their slightly larger size, are more prone to injury, our statistics showing 108 boys to 77 girls in the series.

**Length of Labor.**—Chart 2 shows the length of labor of the mothers. That other factors are present in addition to the forces of labor is shown by the fact that 3 mothers had no labor but were delivered by elective cesarean section. One of these mothers had an attempted induction of labor with thirteen "shots" plus castor oil and quinine before the section was performed. The occurrence of cerebral injury in the baby after cesarean section has been reported by other authors.

Precipitate labor was found in six instances, while the greatest number of mothers required labor of from only one to six hours. Apparently there is an increased tendency to cerebral injury in the children of mothers having less than twelve hours of labor.

**Duration of Pregnancy.**—There were 125 babies delivered at full term while 5 were thought to be post mature. Fifty-five infants or 30 per cent were definitely

Distribution of Parity

Parity of Mother	No. of Cases
I	106
II	29
III	27
IV	8
V	3
VI	4
VII	2
VIII	3
IX	1
X	1
Unknown	1

premature. It has been recognized for some time that in the premature baby, with its fragile blood vessels, cerebral injury is more likely to develop. This study emphasizes that the prevention and management of the premature labor is one of the essentials in the prevention of cerebral injury in the newborn.

Type of delivery is illustrated in chart 3. In those cases in which presentation was known, there were one hundred and sixty-three vertex, three face and seven-teen breech presentations.

**Mature and Postmature Group.**—Included in these were eighty-two spontaneous deliveries, thirty-two forceps deliveries, thirteen breech deliveries (including forceps on the after-coming head in 2 cases) and three cesarean sections. One of the cesarean sections was

From the Departments of Obstetrics and Orthopedic Surgery, Indiana University School of Medicine.

Read before the Section on Obstetrics and Gynecology at the Ninety-First Annual Session of the American Medical Association, New York, June 13, 1940.

1. Schreiber, Frederic: Apnea of the Newborn and Associated Cerebral Injury: Clinical and Statistical Study, *J. A. M. A.* 111:1263-1269 (Oct. 1) 1938.

2. Cole, W. C. C.; Kimball, David C., and Daniels, L. E.: Etiologic Factors in Neonatal Asphyxia, *J. A. M. A.* 113:2038-2044 (Dec. 2) 1939.

performed two weeks after the calculated date for delivery. One patient was born by cesarean section after the mother had had several hours of labor and was several weeks past her calculated date for delivery. Definite spells of cyanosis were present from birth. The third section in this group was done after fourteen hours of labor. Here no resuscitation was necessary, and no cyanosis was present.

AGE OF MOTHER	NUMBER OF CASES	PCT. TOTAL
15-20	33	18%
20-25	60	32%
25-30	39	20%
30-35	26	14%
35-40	15	8%
40-45	7	4%
Not Given	5	

Chart 1.—Age distribution of mothers.

The surprising feature in the full term group is that 83 of the mothers had spontaneous deliveries, emphasizing the fact that the normal forces of labor may be, and often are, responsible for cerebral injuries. In some instances these injuries are not preventable. In some cases it is possible that an indicated forceps operation might have prevented injury; yet the patient finally had a spontaneous delivery.

In mothers having tumultuous labor or pituitary-like pains, anoxemia may be produced in the infant by the almost continuous systole of the uterus, not permitting fresh blood to the capillary bed of the placenta. In these cases pharmacologic analgesia or anesthesia may actually benefit the baby by decreasing the anoxemia and the actual force to which the infant is subjected.

*The Premature Group.*—In this group there were 25 cases of from six to seven months' gestation, 26 cases of from seven to eight months, and 4 cases of slightly more than eight months. Of this number, 46 were delivered spontaneously, 3 were delivered by low forceps, 4 were delivered by breech extraction and 2 were delivered by cesarean section. It was impossible to obtain accurate weights of the babies in the majority of the cases, but the smallest was apparently 1,280 Gm.

One of the cesarean sections in this group was done on a patient with eclampsia at eight months. The other section, as mentioned previously, was done after attempted induction had failed. Another mother with eclampsia was cared for at our University Maternity Hospital and delivered from below. The mothers of two infants had toxemias of late pregnancy and were delivered at seven and one-half and eight months.

Five children in this group were of twin births. The first was the second of twins born at seven months. The second was the first of twins delivered at seven and one-half months. The third was one of twins delivered at seven months, the other twin living but one day. Infant 4 was the second of twins delivered by cesarean section, while the fifth was a first twin, delivered by forceps.

As prematurity is a predisposing factor in cerebral spastic paralysis, any complication of pregnancy causing

or necessitating premature labor is indirectly responsible. Toxemia, multiple pregnancy, placenta prævia or abruptio placentae may be listed as indirect factors. The latter two complications may be direct factors because of the production of anoxemia.<sup>3</sup>

The proper conduct of the premature labor is imperative in the prevention of cerebral injury. Prevention of premature labor is of even greater importance. Of the 46 spontaneously delivered mothers in this group, none had episiotomies. We believe it is of more importance for the primipara in premature labor to have an episiotomy than it is for the primipara at full term. Certainly the head of an infant about to be born prematurely should not be permitted to pound against the perineum for more than one hour. It is much better, when there is any appreciable delay, that episiotomy be done and the mother be delivered by the low forceps method, if a perfect application can be made. The choice of analgesia in premature labors is also of much importance.

In our premature group, 39 mothers were primiparas. Of these, 2 had breech deliveries, 2 had low forceps deliveries and the remaining 33 were delivered spontaneously without episiotomy. Of the remainder of the 14 mothers, all had normal deliveries except 2 who had breech presentations. Of these babies there were 4 second born, 2 fourth born, 1 fifth born, 1 seventh born and 2 eighth born.

*The Use of Solution of Posterior Pituitary.*—Unfortunately, solution of posterior pituitary is too widely used for induction and augmentation of labor, in spite of continuous warning from teachers of obstetrics. In 12 mothers of this series, it was used in an attempt to induce labor. In 12 additional cases, it was given during labor. One infant, who was the sixth baby of her mother, was delivered after induction by solution

LENGTH OF LABOR IN HOURS	NUMBER OF CASES
NO LABOR	3
PRECIPITATE LABOR	6
LESS THAN 1 HR.	9
1-6 HOURS	56
6-12 HOURS	39
12-18 HOURS	19
18-24 HOURS	10
24-48 HOURS	24
MORE THAN 48 HRS.	12
UNKNOWN	7

Chart 2.—Length of labor of mothers.

of posterior pituitary. The mother gave a history of each labor's having been induced by solution of posterior pituitary.

Regarding another mother given solution of posterior pituitary during labor, the physician stated that he wanted the baby to be born without instruments. In a third instance, a hypodermic injection was given ten

3. Clifford, Stewart H.: Asphyxia of the Fetus and the Newborn Infant, *Am. J. Obst. & Gynec.* 39: 388-399 (March) 1940.

minutes before the birth of the baby. After the injection there was a continuous pain until the baby was born.

The fact that mothers of 24 out of 185 infants received solution of posterior pituitary either given to induce labor or given in labor before birth of the baby speaks for itself. In 13 per cent of our total number of cases solution of posterior pituitary had been used and was at least in part responsible for the resulting cerebral spastic paralysis.

*The Association of Apnea with Cerebral Injury.*—Attention has recently been called to the fact that apnea is associated with cerebral injury in the majority of cases of the latter. The employment of measures of resuscitation would certainly be positive evidence of apnea; however, many obstetricians routinely use the tracheal catheter to clear the airway of the newborn, so that this does not necessarily mean apnea. In this series of cases, the tracheal catheter was seldom if ever used. Obsolete methods of resuscitation such as spanking and immersion in hot and cold water were the methods chiefly employed. Of the 125 cases at or past term, resuscitation was employed definitely in 52 and was not employed in 69 instances. The remainder were

gave a history of difficult subsequent deliveries with normal babies and 3 had subsequent cesarean sections, 1 of the infants being stillborn.

#### SUMMARY AND CONCLUSIONS

One hundred and eighty-five cases of cerebral spastic paralysis have been studied. Anesthesia and analgesia played little, if any, part in this series. There was an increased tendency to cerebral injury in infants of mothers having less than twelve hours of labor. The greatest number of cases was found in women having normal spontaneous deliveries, while 5 cases followed cesarean section. Thirty per cent of the babies were premature. The role of solution of posterior pituitary in contributing to the incidence of spastic paralysis was studied, as it was used in 13 per cent of the series. Cerebral spastic paralysis was present in many infants showing no clinical evidence of apnea or asphyxia.

1. The proper management of labor constitutes the best prevention of cerebral spastic paralysis.

2. Prevention and treatment of premature labor is the greatest single factor in the prevention of cerebral injury.

3. Solution of posterior pituitary continues to contribute to the incidence of cerebral spastic paralysis.

4. Cerebral injury in the newborn is not always preceded by asphyxia, as shown by the fact that at least half of the cases in this series were not associated with asphyxia.

5. It is our opinion that cerebral spastic paralysis may occur in many cases when labor has been faultlessly managed.

314 and 508 Hume-Mansur Building.

#### ABSTRACT OF DISCUSSION

DR. WARD F. SEELEY, Detroit: For about one hundred years a causal relationship has been known to exist between cerebral spasticity and birth injury. Many observers have reported a high incidence of asphyxia at birth in these cases. More recently the role of cerebral anoxia has been emphasized in the production of degenerative cerebral lesions with clinical manifestations of spasticity, convulsions or mental deficiency. Apnea is merely a clinical accompaniment in some of the cases in which cerebral anoxia may be present at birth. In the same category as asphyxia livida and asphyxia pallida, there is also an asphyxia occulta in which the brain may be wrecked even though there is no evidence of apnea. The fact that resuscitation was not necessary in at least half of the cases in this series should not be "startling" if the thesis of cerebral anoxia is accepted as the etiologic factor in the production of these lesions. External pressure on the fetal head or intracranial pressure from a subdural hematoma may shut off the local cerebral blood supply, causing a stagnant anoxia with cell destruction but without evidence of apnea at birth. Anoxic anoxia secondary to a premature separation of the placenta may have ruined the fetal cerebral cortex without visible birth apnea. Most important from the standpoint of the obstetrician is the histotoxic anoxic effect of analgesia, and analgesia which may be superimposed on already existing anoxic factors. I should like to know what type of anesthesia was used in the five cesarean cases—whether local, spinal or general. If the latter, a cerebral anoxia must be considered as having caused the cerebral degenerative changes since, as both Schreiber and Cole have intimated, asphyxia and cerebral degeneration are more apt to occur with general than with local or spinal anesthesia. The greatest danger to which the premature infant is exposed is a failure of the respiratory mechanism. If other anoxic hazards are added in the form of intervention, anesthesia or analgesia, and a spastic child results, the whole responsibility cannot be placed on the factor of prematurity, entirely ignoring any optional adjuvants. The authors

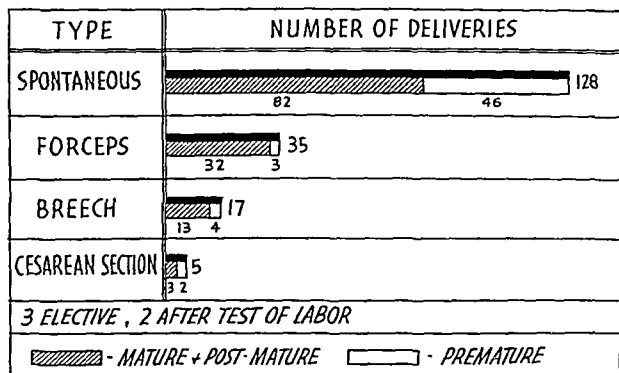


Chart 3.—Type of delivery of mothers.

questionable. The fact that resuscitation was not necessary in at least half of the cases is startling. Cyanosis was absent in 74 of these cases and present in 51. Convulsions occurred in 27 of the mature group and in 5 of the premature group.

In the premature group of 55 cases, resuscitation was not necessary in 33 cases and was necessary in 14 cases, the remainder being doubtful. Cyanosis was absent in 25 cases and present in 22 cases. Therefore, cerebral injuries many times exist in the absence of apnea or asphyxia.

*Preceding and Subsequent Pregnancies.*—In 2 mothers, both secundiparas, the first babies had been born by cesarean section, while their spastic children were second born and normal deliveries. The second of these also had three subsequent normal deliveries with normal babies.

No mother in the series has a second living spastic child though 1 patient, a tertipara in the group, had a subsequent breech delivery with a spastic child who died at six months. Her two preceding children had been normal.

One hundred and twenty of the mothers, including 67 of the primiparas, had no pregnancy after the birth of the spastic child. Fifty-two of the mothers had subsequent normal deliveries with normal babies; 3 others



conclude that cerebral injury in the newborn is not always preceded by asphyxia, but it must be remembered that serious and sometimes preventable cerebral anoxia may be present without any clinical signs of asphyxia at birth.

DR. GERALD W. GUSTAFSON, Indianapolis: As 87.6 per cent of these patients were delivered in the home with a very small amount of analgesia, we have not considered analgesia to be a great factor in this particular series of cases. The second question is the type of anesthesia that was used in these cesarean sections. Few of the latter were done in Indianapolis, the majority being done in smaller communities throughout the state, and I am sure that the majority of the sections were done under ether anesthesia.

## THE USE OF HISTAMINE IN THE TREATMENT OF SPECIFIC TYPES OF HEADACHES

BAYARD T. HORTON, M.D.  
ROCHESTER, MINN.

Headache is undoubtedly among the most frequent ills to which the human flesh is heir. It is a complaint which has been known to mankind since the dawn of antiquity. Few contributions, however, have marked medical progress in this field.

It is not my purpose to review or consider the differential diagnostic features of the various types of headaches and head pains which have been recorded in the literature but rather to describe a new syndrome of vascular headache and to report the results of treatment with histamine. Other less well defined types of headaches have also been treated with histamine and the results will be reported.

This new syndrome of vascular headache, which MacLean, Craig and I<sup>1</sup> tentatively called "erythromelalgia of the head" and which I shall call "histaminic cephalgia" hereafter, was first encountered and recognized at the Mayo Clinic in September 1937. At that time the syndrome had not been described adequately in the literature. The observations which have been made with reference to this specific type of headache warrant its establishment as a distinct clinical entity, classic in its symptomatology and unique in its response to histamine therapy.

Since September 1937, 184 patients with a primary complaint of headache have been treated with histamine. Diagnoses of their condition ran the gamut of the nomenclature of headaches from psychoneurosis to organic lesions. Among these 184 patients were 72 with histaminic cephalgia. The first part of this paper will be confined to consideration of the 72 cases in which most of the classic features of this new syndrome of vascular headache were encountered. The second part will deal with the 112 cases of less well defined types of headache. Of the 72 patients with typical histaminic cephalgia, 45 were men and 27 women; ages ranged from 21 to 76 years. The majority were in the fourth and fifth decades of life. Symptoms had been present for from two months to thirty-five years. Before the cases are reported, however, the clinical picture of histaminic cephalgia must be defined if valid

conclusions are to be drawn. The clinical picture was secured, not from published literature, for little is available, but from actual observations and complaints of patients.

### HISTAMINIC CEPHALGIA—THE CLINICAL PICTURE

Histaminic cephalgia is characterized by a unilateral headache, which usually begins in the later decades of life, is of short duration as it generally lasts less than an hour, commences and often terminates suddenly, tends to awaken the patient at night one to two hours after he has gone to sleep and is frequently eased by the patient sitting up or by standing erect. It is associated with profuse watering and congestion of the eye, rhinorrhea or stuffiness of the nostril, increased surface temperature and, often, swelling of the temporal vessels of the involved side of the head (fig. 1 a and b).

Pain is the outstanding complaint. It is constant, excruciating, burning and boring; it involves the eye, the temple, the neck and often the face. So severe and frequent are the attacks of pain (as often as twenty times a week) that practically every patient had contemplated suicide. The pain is not confined to the distribution of any cranial nerve but has a tendency to conform to the ramifications of the external carotid artery. During and following the attacks, marked tenderness is usually found when pressure is applied over the branches of the external and common carotid arteries. In the first stages of an attack, compression of the common carotid artery and sometimes the temporal artery frequently gives prompt relief. A few patients have discovered for themselves that compression of the artery on the side of the pain gives relief.

Parry<sup>2</sup> first made the discovery and described it fully in 1789.

The pain in all but 3 of the 72 cases of histaminic cephalgia was confined to one side of the head; in 2 of these 3 the whole head was involved, in the other only the occipital region. In 2 of these 3 cases lacrimation of both eyes occurred during attacks. The right and left sides of the heads of patients of both sexes were involved to about the same extent. Attacks were not accompanied by gastrointestinal symptoms or visual disturbances. Some of the patients had had migraine but the majority stated that they did not have periodic headaches in their earlier years. There was no relationship between the menstrual cycle and the bouts of pain. Fifteen of the patients had submitted to various operative procedures for relief of their pain before they came to the clinic. Most of them had had multiple operations. They were disabled by the disorder and had found no relief from the usual methods of treatment.

**Alcohol and Headaches.**—The use of alcoholic beverages precipitated attacks in 28 cases. When this effect had been noticed, patients had become total abstainers, but this did not result in cure. The use of beer, in a few instances, had precipitated attacks. During periods of spontaneous remissions, the use of alcohol would not cause attacks. References have been noted in the early literature regarding the relationship of the taking of alcohol to the production of headache.<sup>3</sup>

**Night Pain.**—In many instances the pain occurred with clocklike regularity, particularly at night. Thirty-one of the 72 patients had attacks of pain only at night.

From the Division of Medicine, the Mayo Clinic.  
Because of lack of space, this article has been abbreviated in THE JOURNAL. The complete article appears in the author's reprints.  
Read before the Section on Practice of Medicine at the Ninety-First Annual Session of the American Medical Association, New York, June 12, 1940.

1. Horton, B. T.; MacLean, A. R., and Craig, W. McK.: A New Syndrome of Vascular Headaches: Results of Treatment with Histamine: Preliminary Report. Proc. Staff Meet., Mayo Clin. 14: 257-260 (April 26) 1939.

2. Parry, C. H.: On the Effects of Compression of the Arteries in Various Diseases, and Particularly in Those of the Head, with Hints Towards a New Mode of Treating Nervous Disorders, Mem. M. Soc. London 3: 77-113, 1792; also Edinburgh M. J. 25: 366, 1826.

3. Living, Edward: On Megrin and Sick-Headache, London, J. & A. Churchill, Ltd., 1873. Parry.<sup>2</sup>

Patients would awaken out of a sound sleep with excruciating pain, night after night and week after week, at a certain hour; they would jump out of bed promptly in order to assume an upright position because, during the bout of pain, the reclining position was intolerable. Many patients had slept propped up on pillows and in rocking chairs for a number of weeks and even months prior to coming to the clinic because they had found that by this means the occurrence of the night pain could often be prevented. Although night pain was characteristic, pain during the waking hours was common. Remissions and exacerbations in many cases happened spontaneously. Most patients had had frequent attacks of pain for a year or more without a remission before coming to the clinic.

**Induced Attacks of Headache.**—In 35 of the 72 cases typical attacks of unilateral pain were induced by the subcutaneous injection of 0.1 to 1.2 mg. of histamine. In most of the other cases, no attempt was made to

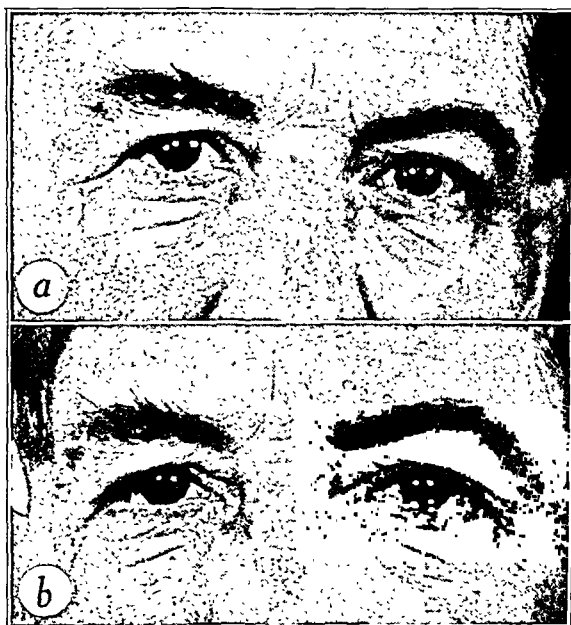


Fig. 1.—Appearance of a man aged 51 (a) before onset of attack and (b) during ten minute spontaneous attack of left "histaminic cephalgia." Watering of the left eye with increased perspiration above the left eyebrow is evident. Attacks had occurred three or four times a week for twenty-five consecutive years. Alcohol precipitated attacks; they could be induced by histamine.

induce an attack. Patients were unable to distinguish between induced and spontaneous attacks, as the two seemed identical. When attacks were induced by the subcutaneous injection of histamine and the patients were under controlled environmental conditions, it was invariably demonstrated by means of electric thermocouples that, as the attack came on, the surface temperature of the involved side of the head rose more rapidly and to a higher level than that of the corresponding side of the head. It was never possible to induce attacks of this character by giving histamine to normal persons.

When epinephrine (1:400,000 solution) was given intravenously to 5 patients who had either induced or spontaneous attacks, relief from pain was prompt. As the blood pressure rose from the resulting vasoconstriction, the pain disappeared. Placing the hand in ice water also immediately stopped the attacks of 4 additional patients. These 4 patients were hyperreactors to

the cold pressor test,<sup>4</sup> and relief was the result of rise in blood pressure from reflex vasoconstriction. These observations seem to indicate that the head pain is on a vasodilating basis.

#### REPORT OF TYPICAL CASES OF HISTAMINIC CEPHALGIA

**CASE 1.—History.**—A woman aged 37 registered at the clinic Sept. 7, 1937, complaining of attacks of severe pain on the right side of the head and face. These episodes came on with clocklike regularity at night and night after night had awakened her at the same time, usually between 3 and 4 a. m. The pain often persisted until 10 or 11 a. m., after which time she generally was free from distress. During attacks her right eye watered and was congested, and there was stoppage of the right nostril. The taking of alcohol precipitated earlier attacks. The pain was made worse by stooping over. There was a sensation of throbbing in the involved region, but trigger zones were never present. The first episode of this character had occurred in 1920 and lasted for two weeks. Later episodes appeared in 1929 and in 1934. Nausea, vomiting and scotomas were never present. She had taken as many as 24 tablets of 5 grains (0.3 Gm.) each of acetylsalicylic acid in one night without relief. The application of ice packs to the right side of the head during attacks had given partial relief, and the intravenous administration of 0.2 to 0.3 mg. of ergotamine tartrate (gynergen) had relieved her. Physical and neurologic examinations revealed nothing significant except considerable tenderness over the right carotid and temporal vessels as well as tenderness over the upper part of the neck. This tenderness was especially noticeable immediately after attacks. The blood pressure measured in millimeters of mercury was 115 systolic and 70 diastolic. The blood counts were normal and the serologic test for syphilis gave negative results. Roentgenograms of the thorax, skull and sinuses revealed negative results.

**Special Studies.**—The patient was observed during a spontaneous attack under controlled environmental conditions. The temperature of the room was 78 F. and the humidity was 40 per cent; the surface temperature of the patient's right temporal region was 34.4 C. (93.9 F.) at the height of the attack, whereas the surface temperature of the corresponding left temporal region was 33 C. (91.4 F.). Over the right zygoma the surface temperature was 34 C. (93.2 F.), and over the left zygoma 32.8 C. (91 F.). Ten minims (0.61 cc.) of epinephrine (1:1,000 solution), given subcutaneously, produced prompt relief.

Under the same controlled environmental conditions when the patient was without pain, the surface temperature of her right temple was 32.5 C. (90.5 F.) and of the left temple 31.5 C. (88.7 F.). One ounce (30 cc.) of alcohol was given by mouth. Forty-five minutes later the surface temperature of the right temple had increased to 34.3 C. (93.7 F.) and the left temple to 32.5 C. (90.5 F.). At this point an attack of pain developed, similar in every respect to a spontaneous attack. Compression of the common carotid artery on the right side relieved the pain, but it promptly recurred when pressure was removed. Ten minims (0.61 cc.) of epinephrine (1:1,000 solution) given subcutaneously produced prompt relief. Attacks were induced and the pain was relieved many times in this manner. The third time epinephrine (1:200,000 solution) was given intravenously and relief from pain was even more immediate.

Subcutaneous injection of 0.5 mg. of histamine precipitated an attack. In order to study the various phenomena associated with the attacks, the same quantity was given on several days. Succeeding attacks seemed progressively less severe and more difficult to precipitate. The possibility of desensitization with histamine was thus suggested. The patient then was desensitized with 0.1 mg. of histamine subcutaneously twice a day for approximately three weeks. After the first five days of this treatment she was free from attacks. She reported on May 17, 1940, that she had not had an attack since she left the clinic. She had a recurrence of the pain in the right side of the head

4. Hines, E. A., Jr., and Brown, G. E.: A Standard Test for Measuring the Variability of Blood Pressure: Its Significance as an Index of the Prehypertensive State, *Ann. Int. Med.* 7: 209-217 (Aug.) 1933.

in August 1940. It followed the hypodermic injection of morphine for relief of abdominal cramps. She was again desensitized with histamine and was again free from headache on Sept. 22, 1940.

It was noted in this case that after several injections the histamine seemed to lose its power to reproduce the pain. It occurred to me that these two phenomena might be related and that the gradually increasing resistance to histamine might in some way alter the phenomena of vasodilatation intrinsically associated with the appearance of pain in the spontaneous headache. It was in this manner that the desensitization treatment of histamine for this type of headache had its origin.

**CASE 2.—History.**—A woman aged 32, who registered at the clinic March 15, 1939, complained chiefly with reference to headaches over the left frontal and temporal regions associated with swelling about the left eye, drainage from the nose and congestive features in the chest. They invariably came

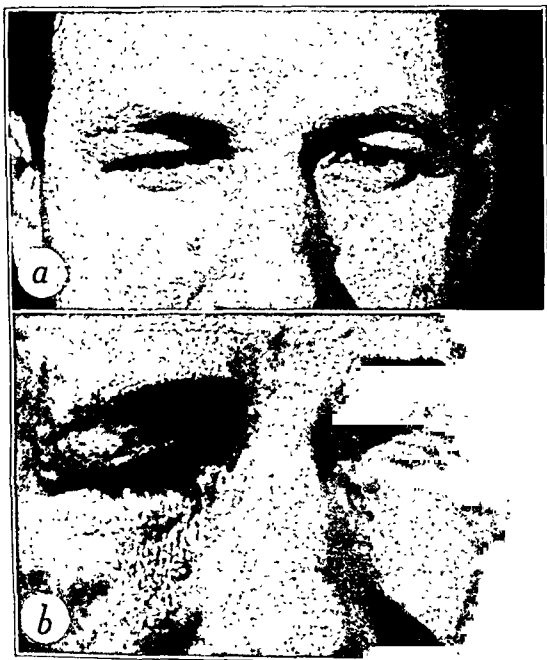


Fig. 2 (case 3).—Appearance of the eyes (a) before the onset of the attack and (b) during an attack induced with histamine. The swelling around the right eye and lacrimation of the right eye may be noted.

on at night and for two years she had slept in a chair or propped up in bed, as the erect posture tended to make the attacks less severe. Nausea, vomiting and scotomas had not been observed during severe attacks of pain. She had a sensation of increased heat in the left side of the head during an attack.

Routine physical examination and laboratory studies gave essentially negative results. Her blood pressure was 130 mm. systolic and 88 mm. diastolic.

**Special Studies.**—With the environmental conditions controlled as described in case 1, the patient was given 0.3 mg. of histamine acid phosphate subcutaneously. Rather marked flushing of the face, a choking sensation in the throat and throbbing in the left side of the face developed. Four minutes after injection of the histamine, pain developed in the left supraorbital region which she stated was of the same type as that which she had previously had at home except that it was milder. The pain increased in severity, both eyes began to water and the lids became swollen. The nose became congested and watered profusely. The surface temperature of the right temporal region increased 1.9 degrees C. (3.4 degrees F.), whereas that of the left temporal region increased 2.9 degrees C. (5.2 degrees F.). The induced attack persisted for approximately thirty minutes.

The patient was given 0.025 mg. of histamine subcutaneously twice daily; the dose was increased gradually, so that by the end of eight days she was receiving 0.1 mg. twice daily. This dosage was continued for three weeks. The attacks became less frequent and less severe after the first five days of treatment, and by the end of the ninth day the patient was entirely free from attacks and was able to sleep flat in bed without discomfort.

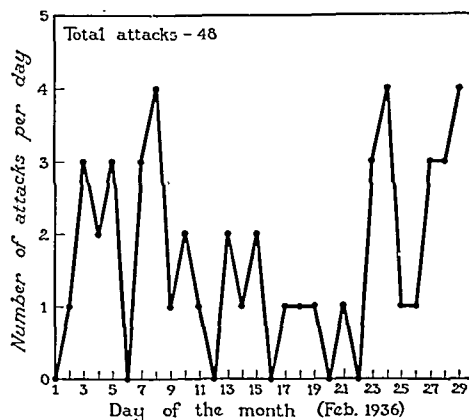


Fig. 3 (case 4).—Daily incidence of attacks of "histaminic cephalgia."

She had no additional treatment after leaving the clinic and remained well for three months. She then had a recurrence of pain on the left side. She again took a similar series of histamine injections twice daily for two weeks and was free from attacks for the next eight months. On recurrence of attacks which were identical to the original attacks, she was again desensitized with histamine and a maintenance dose of 0.1 mg. of histamine was given twice a week. The final report from her, dated May 10, 1940, stated that she was well.

**CASE 3.—History.**—A man aged 32, who registered at the clinic Aug. 14, 1939, complained chiefly at that time with reference to headaches which he had had for seventeen years. The average attack lasted for from thirty to fifty minutes. With the onset of pain, the right eye watered profusely but never became red.

**Special Studies.**—A typical attack of right hemicrania, in every way identical with his spontaneous pain, was produced by the subcutaneous injection of 1.1 mg. of histamine (fig. 2 a

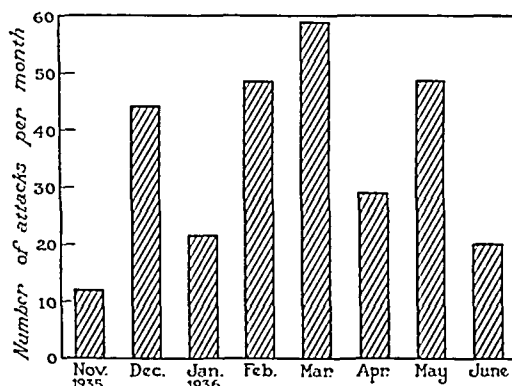


Fig. 4 (case 4).—The monthly incidence of attacks of "histaminic cephalgia" for eight months.

and b). This quantity was given in broken doses over a period of approximately twenty minutes, 0.2 to 0.3 mg. being given at each injection. The attack which was produced lasted fifty-five minutes.

**CASE 4.**—A man aged 43, who registered at the clinic April 8, 1940, complained chiefly with reference to pain of the left side of the face, which localized around the left eye and the second division of the fifth nerve. Symptoms had begun in May 1934. Since that time he had had almost daily attacks except for

two periods of spontaneous relief from June 1938 to April 1939 and from June 1939 to March 8, 1940. The attacks, although they occurred throughout the entire year, tended to be worse in the spring. Shortly after his attacks had begun, he noted that a cocktail would precipitate the pain and, for that reason, he had refrained from the use of alcohol. During the two periods of spontaneous relief, he was able to take alcohol without any difficulty.

The average attack came on at night, usually one and a half hours after the patient had gone to bed, and was characterized by severe, excruciating pain in the left side of the face, and profuse watering of the left eye. In the severe attacks, drainage from the left side of the nose occurred. The attacks had all been alike but had varied in intensity. The average duration of the pain was from ten to fifteen minutes. He kept a diary of his attacks from October 1935 to June 1936 (figs. 3 and 4). He had three hundred and five attacks during this period. The largest number which occurred in a given day was six.



Fig. 5 (case 5).—Appearance of patient and eyes (a) before the onset of an attack and (b) during an induced attack of "histaminic cephalgia," in which the patient is pointing to the site of his pain, which was chiefly localized in the right temporal region.

The following special operative procedures had been carried out without benefit: In May 1935, 4 cc. of 88 per cent alcohol in solution of procaine hydrochloride had been injected into the second division of the left fifth nerve at its point of origin. Later in 1935 the left sphenopalatine ganglion had been injected with alcohol and procaine hydrochloride. In March 1936 the left cervicothoracic sympathetic nerves had been blocked by a paravertebral injection of procaine hydrochloride, but his attacks had become much more frequent and more severe. A general anesthetic had to be given for relief. In April 1936 an operation had been performed on the left sphenoid sinus without benefit. In June 1936 a window was made in the maxillary sinus on the left side, but this gave no relief from attacks.

When the patient was admitted to the clinic in 1940 his attacks were so frequent and so severe that he was sent to the hospital, where examination was carried out. Routine physical, laboratory and neurologic examinations revealed nothing

significant. Shortly after he had had a spontaneous attack, the subcutaneous injection of 0.7 mg. of histamine failed to induce an attack. Twenty-four hours later, however, 1.0 mg. of histamine given subcutaneously produced an attack. Desensitization with histamine was started on April 13, and within a week he was entirely free from pain. He was dismissed from the clinic April 27, 1940, with instructions to take 0.1 mg. of histamine twice a week for an indefinite period. He reported on May 30, 1940, that he had remained entirely free from attacks, although he has been working harder than usual and again on Oct. 25, 1940, that he was perfectly well.

**CASE 5.—History.**—A patient had had his first attack of severe right hemicrania at the age of 14 years. It had come on at 2 a. m. and lasted for about half an hour. Since that time he had had a series of severe attacks each spring and each fall and occasionally in the summer. The average attack in 1939 when the patient was 36 years old lasted from one and a half to seven hours and almost invariably came on at night. The pain was only on the right side of the head. During attacks disturbance of vision and nausea or vomiting did not occur unless he swallowed a handful of pills in an attempt to get relief. The right eye watered profusely but did not become injected; the right nostril became plugged. The pain was much worse if lacrimation did not develop in the right eye. The pain was localized to a spot about 2 cm. in diameter in the right temporal region (figs. 5 and 6) but by 1939 it tended also to spread over the entire right side of the head distal to this region and down over the angle of the jaw. It was so severe that he frequently banged his head against the floor. He likened the pain to that which might be experienced if a hand were being slowly crushed in a vice. In the free intervals in a series of attacks, which lasted for several weeks, alcohol or beer taken by mouth promptly brought on the pain. During remissions, he could take alcohol without difficulty.

A change in environmental temperature often precipitated an attack. Morphine, when taken hypodermically, did not give relief. Acetylsalicylic acid, 20 grains (1.3 Gm.) gave more relief than any other drug. He had never been able to hold a job because the attacks occurred so frequently and were so severe.

The patient was 31 years of age when he first came to the Mayo Clinic, July 3, 1934. Physical and neurologic examination gave essentially negative results. The blood pressure was 120 mm. systolic and 80 mm. diastolic. Because the patient insisted, a right cervicothoracic sympathetic ganglionectomy and trunk resection was performed on July 12. Following this procedure, he had only mild attacks which lasted for fifteen or twenty minutes every month or so.

On each of the twenty-two days prior to his second admission, Sept. 2, 1936, however, he had had severe attacks which lasted for from four to six hours. These came on shortly after midnight. The severe paroxysms of pain made it imperative that something be done. Accordingly on Sept. 4, 1936, the middle meningeal artery was explored through a subtemporal craniotomy. It was found to be large and tortuous and to have a particularly large posterior branch. The artery was dissected free and ligated. Three days later encephalography gave negative results.

The patient's final admission to the clinic was Aug. 11, 1939. He had been having severe attacks daily and sometimes three or four a day during the previous three weeks. A general examination at this time gave negative results and the neurologic examination indicated only the presence of a right Horner's syndrome.

After attacks ceased, the skin over the right temporal region was extremely tender. The patient preferred to sit up rather than lie down during the day and night because posture seemed to be an important factor in precipitating the attack. However, sleeping in a semisitting position did not prevent the occurrence of attacks.

**Special Studies.**—A typical attack of right hemicrania was produced by the subcutaneous injection of 1 mg. of histamine (figs. 5 and 6). It was identical in every respect to the spon-

taneous attacks which were observed. The patient was unable to distinguish between the two. Pain was confined to the right side of the head.

Because of the frequent and severe occurrence of pain, histamine desensitization was started Aug. 14, 1939. Subcutaneous injections were given every six hours day and night. The initial dose was 0.01 mg., and the dosage was increased gradually up to 0.1 mg. by the end of seven days. His attacks after the first two days of this therapy became less frequent and less severe and disappeared by the ninth day. The final report from him, dated May 27, 1940, stated that he had not had an attack of pain since leaving the clinic.

#### DIFFERENTIAL DIAGNOSIS

The syndrome of histaminic cephalgia need not be confused with that of classic migraine. Patients with histaminic cephalgia have frequent short attacks of pain which usually can be measured in terms of minutes or hours and which usually come on suddenly and disappear in a like manner. The attacks begin later in life and are not associated with nausea, vomiting or visual disturbances. There is no hereditary background for the occurrence of these attacks. On the other hand, patients with migraine have attacks of longer duration which almost invariably are accompanied by nausea, vomiting and visual disturbances. Furthermore, at least 85 to 90 per cent of persons with migraine state that one or more members of the family have had migraine. Histaminic cephalgia is not to be confused with trigeminal neuralgia because trigger zones which are found invariably in the presence of trigeminal neuralgia are absent. The pain in trigeminal neuralgia follows the distribution of the first, second or third division of this nerve, whereas the distribution of the pain in histaminic cephalgia is not confined to the anatomic distribution of any cranial nerve but seems to correspond more or less to the anatomic ramifications of the external carotid artery.

#### TREATMENT

The object of treatment is, first, to free the patient from pain, which usually can be accomplished without any great difficulty; second, to determine the proper maintenance dosage. Histamine diphosphate is the drug employed. To attain the first of the foregoing objectives, a "desensitization" program is inaugurated.

The term "desensitization" is used here in the broadest sense. No specific allergic or hypersensitive states have been definitely demonstrated to be related to the symptoms of the patients. The prolonged favorable effect of repeated small doses of histamine in these cases suggests that the action of the drug is in the nature of a desensitization.

Treatment is given according to the following schedule: The contents of a 1 cc. ampule of histamine diphosphate (0.275 mg.) is equivalent to 0.1 mg. of histamine base. Ampules of this character are now on the market. (All doses are given subcutaneously.) The quantity given at each injection is as follows: first injection, 0.25 cc.; second, 0.30 cc.; third, 0.35 cc.; fourth, 0.40 cc.; fifth, 0.45 cc.; sixth, 0.50 cc.; seventh, 0.55 cc.; eighth, 0.60 cc.; ninth, 0.65 cc.; tenth, 0.70 cc.; eleventh, 0.75 cc.; twelfth, 0.80 cc.; thirteenth, 0.85 cc.; fourteenth, 0.90 cc.; fifteenth, 0.95 cc.; sixteenth, 1.00 cc.; seventeenth, 1.00 cc.; eighteenth, 1.00 cc.; nineteenth, 1.00 cc.; twentieth, 1.00 cc.

If, at any time, the patient notices slight flushing of the face or any other symptoms indicating subjective or objective response to the drug, the next dose should

be reduced 50 per cent. An attempt then is made gradually to increase the dose again.

These increasing subcutaneous injections are administered twice daily for approximately ten days to three weeks. After the patient is free from attacks, the second phase of the problem is to prevent future attacks. This can best be accomplished by giving each patient a proper maintenance dosage. This will consist in giving the patient approximately 1 cc. of histamine diphosphate (0.275 mg. of histamine diphosphate) one to three times weekly. The average patient will probably require two injections weekly, whereas a few patients apparently do not require a maintenance dose. I have had many letters of complaint from physicians telling me of their difficulties, and invariably these difficulties have arisen because the patient had been given an overdose of the drug. Injections must be given subcutaneously, not intracutaneously or intravenously. It is easier to give the drug correctly than incorrectly.



Fig. 6 (case 5).—Close-up of patient: c, before the onset of an attack; d, lacrimation of the right eye with tears flowing down the right cheek and slightly increased perspiration above the right eye.

#### RESULTS OF TREATMENT OF HISTAMINIC CEPHALGIA

*Histamine.*—The 63 patients with histaminic cephalgia who were desensitized with histamine will be considered in two groups. Fifty-one of the 63 patients had all the signs and symptoms of typical histaminic cephalgia, whereas 12 had some atypical features. For that reason the results will be reported separately. In 48 of the 51 typical cases, complete relief of symptoms was obtained for varying periods after desensitization. Concerning 3 of these patients, follow-up information is not available. Information received less than a month before June 1, 1940 indicated that 27 patients considered themselves perfectly well. Three additional patients were perfectly well when they were last heard from, approximately sixteen months earlier. Eighteen were still having headaches, but their attacks were much less frequent and much less severe than formerly. Five of the patients who were perfectly well had had no treat-

ment since they left the clinic. The longest period which had elapsed without treatment being given was thirty-three months. Ten of the 27 patients who considered themselves perfectly well were receiving a maintenance dose of 0.1 mg. of histamine either once or twice weekly.

Of the 12 patients who had somewhat atypical signs and symptoms of histaminic cephalgia, 4 were relieved completely of their symptoms at the time of dismissal from the clinic and remained well for periods varying from one month to nine months. One patient was still free from attacks at her last report May 10, 1940, or about two months after dismissal. She had typical histaminic cephalgia except that the pain was located in the occipital region. The other patients in this group obtained from 50 to 90 per cent relief of pain immediately after completion of treatment but had recurrences, which most stated were less frequent and less severe than their former attacks.

*Histaminase.*—Because such excellent results had been obtained from the use of histamine in this group of headaches, it was decided to treat 9 patients with typical histaminic cephalgia with histaminase by mouth. Typical attacks were reproduced by the giving of histamine subcutaneously in 3 subjects. These 9 patients

*Results of Treatment of Various Types of Headache with Histamine*

Group	Cases	Hemicrania	No Relief		Less Than 50 per Cent Relief		More Than 50 per Cent Relief	
			Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
1	44	4	20	45.5	12	27.3	12	27.3
2	36	9	17	47.2	10	27.8	9	25.0
3	13	8	6	46.2	6	46.2	1	7.7
4	19	..	9	47.4	5	26.3	5	26.3
Total	112		52	46.4	33	29.5	27	24.1

were all having from one to three attacks each twenty-four hours and had had to stop work because of their frequent bouts of pain. Eight obtained excellent results from the use of this drug. The longest period without recurrence to June 1, 1940 was ten months; the shortest, one month.

#### HISTAMINE TREATMENT OF OTHER TYPES OF HEADACHE

As previously stated, 184 patients with a primary complaint of headache have been treated with histamine. Among these were 112 whose headaches had none of the features of histaminic cephalgia. The only common features of the headaches of the patients constituting this group of 112 cases were the long duration of symptoms, resistance to ordinary forms of treatment, the willingness on the part of the patients to devote two or three weeks to treatment and the disabling intensity of symptoms. Many of the patients were unable to work because of frequent and severe headaches. They remained for treatment because they insisted that something be done to relieve them of their attacks. An analysis of the clinical types within this group of 112 cases and their response to therapy leads to some well defined conclusions.

All of these patients received subcutaneous injections of histamine (0.05 to 0.1 mg.) twice daily. The usual course consisted of thirty to fifty injections, although some patients received more than one course. Eighty-two of these patients received no other treatment. The

remaining 30 received, in addition, histamine intravenously or histaminase orally. In all cases, however, the subcutaneous desensitization with histamine was the basic therapy. Fifty-three of these patients were observed at intervals or reported by letter for more than six months, and 72 for more than three months. Most of those patients who did report or return for observation within three months did not receive any relief even temporarily; this made further observation unnecessary for evaluation of therapy. A few patients who received moderate relief were not under observation or heard from for more than two months.

Three arbitrary categories of improvement were established for the sake of this study. These are as follows: (1) no improvement; (2) less than 50 per cent relief; in this group are included cases in which relief was not known to have lasted more than two months; and (3) more than 50 per cent relief; in this category are included a few in which complete relief lasted for as long as a year. The cases were divided on clinical grounds into four groups. Grouping criteria were broad and arbitrary, as follows:

In group 1 were included the cases of hemicrania with the prominent features of migraine. Two or more of the following features were present in each case: (1) attacks associated with vomiting, of consistent nature and duration; (2) prodromes or scotomas; (3) hemicrania among at least 2 other members of the family; (4) duration of the typical attack for thirty-six hours or more, and (5) complete freedom from pain at intervals. Cases of apparent psychic predisposition were not included in this group. In group 2 were the cases of headache with prominent psychogenic features. In group 3 the headache was associated with known cephalic organic disease. Cases of such conditions as brain tumor, latent cerebrospinal syphilis, cerebral cortical atrophy, marked hypertension and those in which multiple operative procedures had been performed were included. In group 4 were the miscellaneous cases. In some cases clinical details were inadequate or too confused to classify otherwise, but in this group were included 5 cases in which the pain consistently was localized to a very small region, such as one eyeball. The results of treatment in these groups of cases are given in the accompanying table.

The trend of improvement in each clinical group closely followed that shown in the sample as a whole. In view of the diverse characteristics of the clinical conditions typified by these groups, this observation suggests either that histamine therapy had uniformly beneficial effects on each type, which is hardly credible, or that it had no effect on any group included in this total sample. Lacking a control group of untreated or placebo treated patients, the spontaneous remission rate is conjectural, but at all events the improvement noted does not exceed a reasonable expectation of spontaneous relief, especially as it is likely that most patients consulted the clinic at the peak of their symptoms.

In the psychogenic group (group 2) a greater or more prolonged incidence of relief than that of the other groups was not noted. This implies that, as administered at the clinic, histamine is not an effective psychotherapeutic or suggestive measure. From this critical study histamine therapy does not appear to be particularly effective in treatment of the commoner types of severe headache, although the majority of the subjects felt that they obtained temporary benefit.



## SUMMARY AND CONCLUSIONS

Seventy-two cases illustrate a new syndrome, "histaminic cephalgia," associated with clinical and laboratory evidence of vasodilatation. This type of headache represents a distinct clinical entity which is unique in its symptomatology and its response to histamine therapy. Attacks can be induced at will with given amounts of histamine and can be eradicated by desensitization with histamine. A maintenance dose of 0.1 mg. of histamine twice weekly is usually necessary to prevent recurrence of attacks. The spectacular manner in which patients respond indicates that histamine treatment is as specific for this syndrome as insulin is in the treatment of diabetes mellitus. The observations which have been made at the clinic since September 1937 and the results which have been obtained by means of histamine therapy justify this conclusion. Surgical intervention for the relief of this type of pain seems to be unwarranted. Histamine therapy is not effective in treatment of commoner types of severe headache.

For purpose of classification, the term "histaminic cephalgia" is suggested as descriptive of the entity with which we have been dealing. This term seems logical in view of the fact that patients are unable to distinguish between attacks induced with histamine and spontaneous attacks. Furthermore, the disease can be promptly eradicated by desensitization with histamine.

## ABSTRACT OF DISCUSSION

DR. EMANUEL LIBMAN, New York: Dr. Horton has presented an original piece of work in an admirable way. He has made a beginning in sifting out the cases of "migraine." As one looks up what the best writers have said, one will find a great deal of confusion. Even headaches evidently due to sinusitis have been included. The syndrome described by Dr. Horton differs from migraine. It comes on at a much later period of life and many of the typical phenomena of migraine are missing. I would not lay too much stress on the influence of alcohol, because it has a tendency to increase a number of varieties of headaches, especially the headache due to sinusitis. Flushing has been described in migraine. Oppenheim noted it in "vasomotor cephalgia," a condition which may be associated with urticaria. This flushing is not accompanied by lacrimation. In headaches due to sinusitis one can have lacrimation, but it is usually not as marked or it does not come on as acutely and disappear as abruptly. Headaches due to sinusitis may be periodic and may occur only late at night, but under such conditions fever and other toxic phenomena are usually present. It would be of interest to learn the origin of the intoxication in the cases described by Dr. Horton. Has any relationship to the carotid sinus been noted? Dr. Horton has found histamine of value in Ménière's disease. As a result of the varied investigations he is carrying out on the therapeutic value of histamine, we may expect him to provide us with other valuable leads. This and other contributions that Dr. Horton has made show that a wide field remains for purely clinical research. Often young men are told that there are now no fruitful fields in clinical medicine and pathology. This is wrong. There are many avenues of progress open in these disciplines. As biochemistry, experimental physiology and related subjects advance, changes must be made in our clinical classification and in our concepts of pathologic changes. If the experimental work with histamine had not been done, Dr. Horton could not have segregated his syndrome. While we all realize the continually increasing importance of animal experimentation, we must be careful not to stress the need of animal experimentation when clinical studies alone may suffice or give results not obtainable by animal experimentation.

DR. LEONARD G. ROWNTREE, Philadelphia: I think we are listening to medical history in the making. Dr. Horton has

recognized a new disease, he has defined it, named it, determined its pathogenesis, reproduced it in subjects at will and has devised a cure for it. I have never heard of any device, recognized and introduced so handily, where one man, with deepness, quickness and dispatch, has handled the whole situation personally, and this marks Dr. Horton as a clinician of distinction. This disease is a syndrome which may be defined as a regularly recurring, severe and often excruciating paroxysmal unilateral headache of brief duration, affecting during the night middle aged and elderly persons and awakening them from their sleep. The pain conforms to the distribution of the external carotid artery and is due to vasodilatation secondary to the release of histamine and can be produced at will in the subjects of this disease. The attacks are accompanied by signs of congestion in the area involved, lacrimation, rhinorrhea, the subjective feeling of heat locally, actual increase of temperature as determined by the thermometer, and swelling of the temporal arteries. These attacks are as distinct as migraine or as *tic douloureux*, and they are related to neither. It represents a histamine type of attack. It is reproduced by histamine. It is brought out through desensitization, and it is controlled by histaminase. I believe he is right, that histamine is a specific, as insulin is in diabetes. Dr. Horton has been a student for many years of vascular disease, particularly peripheral vascular disease, and also of the drug histamine. This is the outgrowth of a natural flair for investigation and good training, careful study of patients, an abundant opportunity to study patients and, above everything else, intellectual thinking. I would like to ask if he can give us any idea as to the nature of the local mechanism, because there must be one, and what has come to pass when he has attempted this same experiment in cases in which the sympathetics to this region have been removed for other purposes.

DR. BAYARD T. HORTON, Rochester, Minn.: I have attempted to describe only what I have seen and what my patients have told me. Many of my colleagues, especially Dr. A. R. MacLean, have contributed much to the success of this work. The exact mechanism by which this syndrome of vascular headache is produced is not clear. Experimental and clinical data indicate a local release of histamine with resultant vasodilatation which is almost exclusively confined to the ramifications of the external carotid artery. During induced attacks, with patients under controlled environmental conditions, the surface temperature of the involved side of the head invariably rises more rapidly and to a higher level than that of the opposite side of the head. This obviously indicates local vasodilatation. A sensitive carotid sinus has not been noted in this series of patients, nor do I think that it has been responsible for the production of this particular type of headache. I have seen a few patients who had the pain but did not have definite lacrimation. Unilateral lacrimation is a prominent feature in the average case. Prior to coming to the clinic, two patients had undergone cervical sympathectomy for the purpose of eradicating the pain, but they received little or no benefit from this surgical procedure. Desensitization with histamine, however, did eradicate their attacks. Dr. Libman and Dr. Rowntree are right in suggesting that "erythromelalgia of the head" is not an appropriate term to use in describing this syndrome. We originally suggested the term "erythromelalgia of the head" as a descriptive term for this syndrome because of the vasodilating features. In doing so, we regarded the head as a fifth extremity. Dr. Rowntree suggested the term "erythrocephalgia" which I think is better than the one we originally employed. Regardless of the terminology, I doubt whether any syndrome in clinical medicine is more spectacular or clear cut than that which I have attempted to describe. My observations certainly seem to warrant the establishment of this type of headache as a distinct clinical entity. The syndrome lends itself beautifully to experimental study. The attacks can be reproduced so accurately that patients are unable to distinguish between induced and spontaneous attacks. Furthermore, the syndrome can be eradicated promptly by desensitization with histamine. I cannot escape the conviction that the use of histamine in the treatment of this syndrome is as specific as insulin is in the treatment of diabetes mellitus.

## THE ROLE OF CHLORIDES IN ALKALOSIS

FOLLOWING THE ADMINISTRATION OF  
CALCIUM CARBONATE

JOSEPH B. KIRSNER, M.D.

AND

WALTER LINCOLN PALMER, M.D.

CHICAGO

The term "alkalosis" was used originally by Fischler<sup>1</sup> in 1911 with reference to the toxemia of animals with Eck fistulas because the disturbance was attributed to a disproportion between the acid and base in the body. Alkalosis has since assumed increasing significance in relation to various experimental and clinical problems. It was first reported as a complication of the Sippy treatment of peptic ulcer by Grant<sup>2</sup> in 1922, although Sippy himself had previously recognized its occurrence.<sup>3</sup> Its manifestations have now become familiar to most clinicians as a result of the detailed accounts of Hardt and Rivers,<sup>4</sup> Ellis,<sup>5</sup> Gatewood and his associates<sup>6</sup> and others.<sup>7</sup> Despite the fact that the original Sippy powders were mixtures of sodium bicarbonate and calcium carbonate, the systemic effects of alkali administration were attributed entirely to the highly soluble sodium bicarbonate, and the influence of calcium carbonate on the electrolyte balance received only occasional consideration. It was assumed originally that this alkali had little or no effect on the acid-base balance and mineral metabolism.<sup>8</sup> A recent paper by McGee and others<sup>9</sup> likewise indicated that moderate amounts of calcium carbonate did not significantly alter the acid-base equilibrium. In contrast to these studies are the reports of Wildman,<sup>10</sup> Gatewood and his associates,<sup>6</sup> Cooke,<sup>11</sup> and Cope<sup>12</sup> describing the occurrence of alkalosis in patients receiving only calcium carbonate. In this report we present a further study of the alkalosis following the administration of calcium carbonate and refer particularly to the role of chlorides.

### METHOD OF STUDY

A series of 105 patients with peptic ulcer, including both sexes and of ages from 16 to 78, has been treated with large doses of calcium carbonate during the past three years. Alkalosis, as evidenced by a disturbance

in the acid-base equilibrium, developed in 32 of these. The serum carbon dioxide combining power,  $p_H$  and chlorides and the blood urea nitrogen were determined<sup>13</sup> at different periods during treatment, the number of such determinations varying with the individual case. The normal values for these procedures are carbon dioxide 22 to 30 millimols per liter,  $p_H$  7.35 to 7.45, chlorides 100 to 110 millimols per liter and blood urea nitrogen 9 to 15 mg. per hundred cubic centimeters. In addition to the routine examinations of urine, renal function was estimated by the urea clearance method of Van Slyke.<sup>14</sup> These values are expressed as the percentage of average normal after correction for individual surface area by the method of Peters and Van Slyke;<sup>15</sup> 75 per cent is generally accepted as the lower limit of normal. Although a normal urea clearance may not exclude the possible presence of renal disease,<sup>16</sup> it is considered one of the most reliable measures of renal function in use today.<sup>17</sup>

### CLINICAL ASPECTS

It is of interest to note that no direct correlation existed between the amount of calcium carbonate received and the development of alkalosis. The acid-base balance remained within normal limits in some cases after the ingestion of as much as 48 Gm. daily for forty-two days, while alkalosis occurred in other persons taking as little as 15 Gm. for four days.

The symptoms of alkalosis usually appeared between the third and eighth days of treatment, although in several instances not until after fourteen to eighteen days had elapsed. The significant complaints were a distaste for milk and cream, excessive dryness of the mouth and throat, anorexia, dizziness, headache, weakness, nausea and occasionally vomiting. Tetany, convulsions and coma were notably absent. Symptoms did not occur in several patients despite the presence of a severe chemical alkalosis. There was no consistent correlation between the severity of complaints and the degree of chemical alkalosis, an observation previously noted by Eisele.<sup>18</sup>

### ACID-BASE BALANCE

Alkalosis is characterized chemically by an elevation of the carbon dioxide combining power of the blood, a decrease in the hydrogen ion concentration (rise in  $p_H$ ) and a fall in the serum chlorides. In this series (table 1) the serum carbon dioxide remained within normal limits in 73 patients. In 12 persons with moderate alkalosis the carbon dioxide varied between 31.7 and 37.0 millimols per liter. The serum carbon dioxide was considerably higher in the 20 patients with severe alkalosis, exceeding 40 millimols per liter in 10 cases and reaching a peak of 47.4 millimols per liter in one instance. The serum  $p_H$  paralleled the carbon dioxide. Temporary values of 7.50 were occasionally observed in patients with an otherwise normal electrolyte balance. The  $p_H$  during alkalosis varied between 7.50 and 7.73, exceeding 7.60 in 11 patients. The highest value

From the Department of Medicine, University of Chicago.

Read before the Section on Pharmacology and Therapeutics at the Ninety-first Annual Session of the American Medical Association, New York, June 12, 1940.

1. Fischler, F.: Ueber die Fleischintoxikation bei Tieren mit Eck'scher Fistula. *Der Krankheitsbegriff der Alkalosis*, *Deutsches Arch. f. klin. Med.* **104**: 300, 1911.

2. Grant, S. B.: Tetany: A Report of Cases with Acid-Base Disturbance. *Arch. Int. Med.* **30**: 355 (Sept.) 1922.

3. Personal communication.

4. Hardt, L. L., and Rivers, A. B.: Toxic Manifestations Following the Alkaline Treatment of Peptic Ulcer. *Arch. Int. Med.* **31**: 171 (Feb.) 1923.

5. Ellis, A. W. M.: Disturbance of the Acid-Base Equilibrium of the Blood to the Alkaline Side: Alkalemia. *Quart. J. Med.* **17**: 405 (July) 1924.

6. Gatewood, W. E.; Gaebler, O. H.; Muntwyler, Edward, and Myers, V. C.: Alkalosis in Patients with Peptic Ulcer. *Arch. Int. Med.* **42**: 79 (July) 1928.

7. Jordan, Sara M.: Calcium, Chloride and Carbon Dioxide Content of Venous Blood in Cases of Gastrointestinal Ulcer Treated with Alkalies. *J. A. M. A.* **87**: 1906 (Dec. 4) 1926. Oakley, W. M.: Alkalosis Arising in the Treatment of Peptic Ulcer. *Lancet* **2**: 187 (July 27) 1935. Cooke,<sup>11</sup> Berger and Binger,<sup>20</sup> Jeghers and Lerner.<sup>21</sup>

8. Lovenhart, A. S., and Crandall, L. A.: Calcium Carbonate in the Treatment of Gastric Hyperacidity Syndrome and in Gastric and Duodenal Ulcer. *J. A. M. A.* **88**: 1557 (May 14) 1927.

9. McGee, L. C.; Martin, J. E., Jr.; Levy, Fritz, and Purdum, R. B.: The Influence of Alkalies on Renal Function. *Am. J. Digest. Dis.* **6**: 186 (May) 1939.

10. Wildman, H. A.: Chloride Metabolism and Alkalosis in the Alkali Treatment of Peptic Ulcer. *Arch. Int. Med.* **43**: 615 (May) 1929.

11. Cooke, A. M.: Alkalosis Occurring in the Alkaline Treatment of Peptic Ulcer. *Quart. J. Med.* **4**: 527 (Oct.) 1932.

12. Cope, C. L.: Base Changes in the Alkalosis Produced by the Treatment of Gastric Ulcer with Alkalies. *Clin. Sc.* **2**: 287 (July) 1936.

13. Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry*, Baltimore, William & Wilkins Company, 1931, vol. 2: Serum Carbon Dioxide, p. 283;  $p_H$  (Colorimetrically), p. 796; Chlorides, p. 835; Blood Urea in Nitrogen, p. 554.

14. Van Slyke, D. D., and others: Observations on Courses of Different Types of Bright's Disease and on Resultant Changes in Renal Anatomy. *Medicine* **9**: 257 (Sept.) 1930.

15. Peters and Van Slyke: *Quantitative Clinical Chemistry*,<sup>13</sup> p. 568.

16. Alvings, A. S., and Van Slyke, D. D.: The Significance of Concentration and Dilution Tests in Bright's Disease. *J. Clin. Investigation* **13**: 969 (Nov.) 1934. Van Slyke.<sup>14</sup>

17. Cope, C. L.: The Reliability of Clearance Tests for Renal Efficiency. *Clin. Sc.* **2**: 35 (Sept.) 1935.

18. Eisele, C. W.: Changes in Acid-Base Balance During Alkali Treatment for Peptic Ulcer. *Arch. Int. Med.* **62**: 1048 (June) 1939.

obtained was 7.73. During the course of calcium carbonate therapy the serum chlorides ranged between 95 and 105 millimols per liter in the normal group. In general the chloride curves were mirror images of the carbon dioxide and  $p_H$  curves. In moderate alkalosis the lowest chloride values varied between 81.0 and 96.4 millimols per liter and in 5 cases were below 90 millimols per liter. In severe alkalosis the lowest chloride values varied between 65.8 and 89.4 millimols per liter. In all these cases the chlorides were below 90, and in 5 patients the values were below 80 millimols per liter.

The total base<sup>19</sup> was determined in 20 patients, 12 with a normal acid-base balance and 8 with alkalosis. Contrary to the observations of Cope,<sup>12</sup> the values did not exceed the normal range of 150 to 160 milliequivalents per liter and there was no significant variation in the total base of patients with and without alkalosis. Kiefer,<sup>20</sup> among others, has also noted the occurrence of alkalosis without an appreciable rise in total base.

The serum calcium and phosphorus were determined in 23 patients with a normal electrolyte balance and in 5 patients with alkalosis. All values were normal except in 1 patient with pyloric stenosis in whom a serum calcium of 13.1 mg. was obtained. There was likewise no evidence to suggest that either anemia<sup>21</sup> or hepatic disease<sup>22</sup> played a significant role in the development of alkalosis.

#### RENAL FUNCTION

Among the various theories which have been proposed to account for the development of alkalosis in patients receiving alkalis, greatest emphasis has been placed on antecedent renal disease as a major etiologic factor. Thus, Wilkinson and Jordan,<sup>23</sup> using the sulfate clearance test, noted preceding renal damage in a large number of patients in whom alkalosis later developed. The high incidence of alkalosis in persons with hyper-

TABLE 1.—Acid-Base Balance During Administration of Calcium Carbonate

	CO <sub>2</sub> (mM/L)	Cl (mM/L)	$p_H$
No alkalosis ..... (73 patients)	22-30	95-105	7.35-7.45
Moderate alkalosis ..... (12 patients)	31.7-37.0	81.0-96.4	7.50-7.60
Severe alkalosis ..... (20 patients)	35.0-47.4	65.8-89.4	7.50-7.73

tension and nephritis has also been frequently reported in the literature.<sup>24</sup> Although this relationship is undoubtedly true in many cases, it does not explain alkalosis

occurring in patients without evidence of renal disease,<sup>25</sup> the increase in tolerance to alkalis observed in some cases without improvement in renal function<sup>26</sup> or the absence of alkalosis during therapy in patients with definite renal disease.<sup>7</sup> Normal renal function was present in 22 of 32 cases in the present series before the development of alkalosis. Twelve patients with lowered renal efficiency showed no disturbance in the acid-base balance during treatment. It is interesting to note the absence of alkalosis in 3 patients with hypertension and in one person who had undergone a nephrectomy 26 years previously.

TABLE 2.—Effect of Sodium Chloride on Urea Clearance and Acid-Base Balance  
(Calcium Carbonate Continued—27 Patients)

Normal clearance at all times.....	2
Persistent lowering of clearance.....	2
Return to original clearance.....	23
Return to normal acid-base balance.....	27

It has been reported<sup>26</sup> that during alkalosis the urine frequently contains albumin, casts and red blood cells. In our experience this is unusual. The blood urea nitrogen, however, may rise to high levels and fall with recovery.<sup>27</sup> The blood creatinine, inorganic phosphates and inorganic sulfates may do the same. Urea and sulfate clearances, as well as the excretion of phenol-sulfonphthalein, have been found reduced by various workers.<sup>28</sup> The mechanism by which the decrease in renal function is brought about and the nature of the renal lesion have not been conclusively determined. McCance and Widdowson observed a decided improvement in the creatinine, urea, inulin, phosphate, sodium, ultrafiltrable calcium and magnesium clearances after recovery from alkalosis in a patient with pyloric stenosis. The improvement in the inulin clearance strongly suggested that the major dysfunction was a decrease in glomerular filtration.

In the present series, the urea clearance during alkalosis decreased in 25 of the 32 patients. In 9 cases the clearance dropped to levels as low as 12, 13, 15, 17, 17, 18.5, 20 and 22 per cent of average normal. The blood urea nitrogen rose concomitantly, reaching a peak of 67.6 mg. per hundred cubic centimeters in 1 patient. The urine in 2 patients contained traces of albumin. In a third case, acid urine containing albumin, casts and red blood cells was secreted at the height of the alkalosis. This was the only instance, in this series, of acid urine during alkalosis. The secretion of acid urine under these circumstances has been reported frequently,<sup>29</sup> however, and indicates the presence of severe renal damage. The urea clearance remained unchanged in 7 patients, although in 3 the alkalosis was pronounced. Normal clearance values had been obtained previously

25. Nicol, B. M.: The Renal Changes in Alkalosis, *Quart. J. Med.* 9: 91 (Jan.) 1940. Gatewood, Gaebler, Muntwyler and Myers.<sup>6</sup> Cooke.<sup>11</sup> Wildman.<sup>10</sup> Cope.<sup>12</sup> Footnote 24.

26. These include, among others, Hardt and Rivers.<sup>4</sup> Jordan.<sup>7</sup> Jeghers and Lerner.<sup>21</sup>

27. McCance, R. A., and Widdowson, E. M.: Alkalosis with Disordered Kidney Function, *Lancet* 2: 247 (July 31) 1937. Footnote 7.

28. Wilkinson and Jordan.<sup>23</sup> McCance and Widdowson.<sup>21</sup> Footnote 7.

29. Brown, G. E.; Eusterman, G. B.; Hartman, H. R., and Rowntree, L. G.: Toxic Nephritis in Pyloric and Duodenal Obstruction: Renal Insufficiency Complicating Gastric Tetany, *Arch. Int. Med.* 32: 425 (Sept.) 1923. Gamble, J. L., and Ross, S. G.: Factors in Dehydration Following Pyloric Obstruction, *J. Clin. Investigation* 1: 403 (June) 1925. Gollwitzer-Meier, K.: Tetanie Studien. 111. Die Magen-tetanie, *Ztschr. f. d. ges. exper. Med.* 40: 83, 1924. Steinitz, H.: Ueber chloroprive Tetanie bei Magen-erkrankungen, *Ztschr. f. klin. Med.* 107: 560, 1928. Meyer, Paul: "Uraemie" infolge langdauernden Erbrechen, *Klin. Wchnschr.* 10: 155, (Jan. 24) 1931.

19. Stadie, W. C., and Ross, E. C.: Micro Method for Determination of Base in Blood and Serum and Other Biological Materials, *J. Biol. Chem.* 45: 735 (Oct.) 1925.

20. Kiefer, E. D.: The Interdependence of Gastric Secretion and the CO<sub>2</sub> Content of the Blood and Its Significance in the Alkali Treatment of Peptic Ulcer, *Am. J. Digest. Dis. & Nutrition* 4: 667 (Dec.) 1937.

21. Hubble, Douglas: The Dosage of Alkali, correspondence, *Lancet* 2: 634 (Sept. 14) 1935.

22. Eusterman, G. B., and Balfour, D. C.: The Stomach and Duodenum, Philadelphia, W. B. Saunders Company, 1935, p. 288.

23. Wilkinson, S. A., and Jordan, Sara M.: The Significance of Alkalosis in the Treatment of Peptic Ulcer, *Am. J. Digest. Dis. & Nutrition* 1: 509 (Sept.) 1934.

24. Jordan, Sara M., and Kiefer, E. D.: Factors Influencing Prognosis in the Medical Treatment of Duodenal Ulcer, *Am. J. Surg.* 15: 472 (March) 1932. Rockus, H. L., and Bank, Joseph: Alkalosis and Duodenal Ulcer, *M. Clin. North America* 16: 143 (July) 1932. Shattuck, H. F.; Rohdenburg, E. L., and Booher, Lela E.: Antacids in the Medical Management of Peptic Ulcer, *J. A. M. A.* 82: 200 (Jan. 19) 1924. Way, C. T., and Muntwyler, Edward: Alkalosis: Clinical Problem, *Ann. Int. Med.* 8: 816 (Jan.) 1935. Berger and Binger.<sup>30</sup> Oakley.<sup>7</sup> Hardt and Rivers.<sup>4</sup> Eisele.<sup>12</sup>

in 5 of this group. It is of interest to note that the urea clearance decreased during calcium carbonate therapy in 8 patients without alkalosis, an observation reported also by McGee and his associates.<sup>9</sup> In 4 the clearance had been previously either low or at the lower limit of normal. However, the drop in values varied from 10 to 15 per cent and was of no clinical significance.

There have been relatively few studies reported in the literature on the status of renal function after the subsidence of alkalosis. The evidence available<sup>30</sup> indicates that the kidneys usually recover completely their normal function within several weeks or two to three months. Cope reported the case of a man who had experienced four severe attacks of alkalosis. The renal function, estimated by the urea clearance method, after recovery from the fourth attack was 92 per cent. Jeghers and Lerner,<sup>31</sup> Steele<sup>32</sup> and Berger<sup>33</sup> have noted that in occasional patients the lowered renal function may persist for some time. In the present series, renal function returned to its original level in 23 of 25 patients (table 2). This improvement was noted usually within seven to fourteen days after the onset of treatment. In some patients recovery occurred within two to three days, while in 3 cases one, three and six months elapsed before recovery was complete.

#### TREATMENT

Alkalosis, regardless of cause, is invariably associated with a decrease in the serum chlorides. This relationship is explained by the fact that the total base concentration of the serum is maintained at a relatively constant level. The total base is combined for the most part with chloride and bicarbonate ions and, consequently, a change in the concentration of one of these cations causes a compensatory and inverse alteration in the concentration of the other. In this manner, a normal electrolyte content and normal osmotic pressure of the blood are preserved.<sup>34</sup> Hartwell and Hoguet<sup>35</sup> apparently were the first to use physiologic solution of sodium chloride in the alkalosis of experimental intestinal obstruction, although the beneficial results were attributed by these authors to the administration of fluids. The specific value of sodium chloride in relieving the metabolic disturbance in pyloric and high intestinal obstruction was subsequently established in numerous experimental and clinical studies.<sup>36</sup> The use of sodium chloride in the treatment of alkalosis during alkali ingestion likewise has been found highly effective, although the discontinuance of alkalis undoubtedly has played a major role in the recovery of these patients. Wildman

and Gatewood, in fact, attributed a large proportion of the symptoms of uncompensated alkalosis to the hypochloremia. It has been recognized for some time that the clinical and chemical manifestations of experimental and human salt deficiency<sup>37</sup> closely resemble those of alkalosis arising during alkali therapy. In view of these considerations it seemed to us probable that in calcium carbonate alkalosis the hypochloremia might be the primary factor. If this were true, the addition of sodium chloride should suffice to correct the acid-base balance despite the continuation of alkali. The first opportunity to test this assumption arose in the following case:

#### REPORT OF CASES

CASE 1 (chart 1).—R. F., a man aged 24, a travel agent, entered the hospital after a severe massive hemorrhage from a duodenal ulcer. On the seventh day of calcium carbonate therapy, acid-base studies revealed a mild alkalosis which

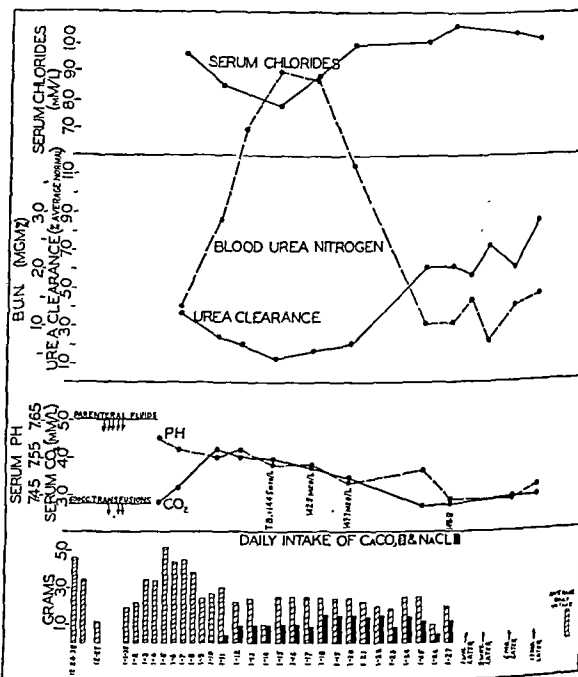


Chart 1.—Effect of sodium chloride and calcium carbonate administration on blood chemistry in case 1.

became severe four days later. Sodium chloride was added to the program on the twelfth day. Despite the continuation of calcium carbonate, the acid-base balance gradually improved and returned to normal after fourteen days of added sodium chloride therapy. The blood urea nitrogen dropped from a peak of 54.7 mg. per hundred cubic centimeters to 10.4 mg. per hundred cubic centimeters, and the urea clearance rose from 13 per cent to 61 per cent of average normal. The patient has shown no further signs of alkalosis despite continued calcium carbonate therapy for a period of two years. The urea clearance is now 85 per cent, and the blood urea nitrogen is 15.3 mg. per hundred cubic centimeters.

30. Berger, E. H., and Binger, M. W.: The Status of the Kidneys in Alkalosis, *J. A. M. A.* **104**:1383 (April 30) 1935. Cooke,<sup>31</sup> Cope,<sup>32</sup> Nicol.<sup>33</sup>

31. Jeghers, Harold, and Lerner, H. H.: The Syndrome of Alkalosis Complicating the Treatment of Peptic Ulcer: Report of Cases with a Review of the Pathogenesis, Clinical Aspects, and Treatment, *New England J. Med.* **214**:1236 (June 18) 1936.

32. Steele, J. M.: Renal Insufficiency Developing During Prolonged Use of Alkali: Report of Case, *J. A. M. A.* **106**:2049 (June 13) 1936.

33. Berger, E. H.: Importance of Kidney Function in Alkalosis, *Northwest Med.* **36**:125 (April) 1937.

34. Peters and Van Slyke: *Quantitative Clinical Chemistry*,<sup>12</sup> vol. 1, p. 1031.

35. Hartwell, J. A., and Hoguet, J. P.: Experimental Intestinal Obstruction in Dogs with Especial Reference to Cause of Death and the Treatment by Large Amounts of Normal Saline Solution, *J. A. M. A.* **59**:82 (July 13) 1912.

36. These include among others:

MacCallum, W. G.; Lintz, J.; Vermilye, H. N.; Legett, T. H., and Boas, E.: The Effect of Pyloric Obstruction in Relation to Gastric Tetany, *Bull. Johns Hopkins Hosp.* **31**:1 (Jan.) 1920.

Dixon, C. F.: The Value of Sodium Chloride in the Treatment of Duodenal Intoxication, *J. A. M. A.* **82**:1498 (May 10) 1924.

Walters, W. D., and Bollmann, J. L.: Experimental Acute Gastric Obstruction, *Arch. Surg.* **13**:578 (Oct.) 1926.

Fistula, Arch. Surg. **13**:578 (Oct.) 1926.  
Gatch, W. D.; Trusler, H. M., and Ayers, K. D.: Acute Intestinal Obstruction: Mechanism and Significance of Hypochloremia and Other Blood Chemical Changes, *Am. J. M. Sc.* **173**:649 (May) 1927.

37. These include among others:

Frouin, A.: Action des chlorures de l'alimentation sur la sécrétion gastrique, *Presse méd.* **30**:1096 (Dec. 20) 1922.

Dragstedt, L. R., and Ellis, J. C.: The Fatal Effect of the Total Loss of Gastric Juice, *Am. J. Physiol.* **93**:407 (June) 1930.

Borst, J. G. G.: Urämie durch Kochsalzmangel, *Ztschr. f. Klin. Med.* **117**:55, 1931.

McCance, R. A., and Widdowson, E. M.: The Secretion of Urine in Man During Experimental Salt Deficiency, *J. Physiol.* **91**:222 (Nov. 26) 1937; *ibid.*<sup>24</sup>

Poll, Daniel, and Stern, J. E.: Untoward Effects of Diuresis with Special Reference to Mercurial Diuretics, *Arch. Int. Med.* **58**:1027 (Dec.) 1936.

Lyall, Alexander, and Nicol, Bruce M.: Gastric Secretions in Hypochloremia, *J. Physiol.* **96**:21 (June 14) 1939.

As a result of these observations, 27 patients with alkalosis during the administration of calcium carbonate have been treated similarly. The quantity of sodium chloride prescribed varied from 3 to 15 Gm. daily, although the minimum effective dose seems to be about 5 Gm. Clinical improvement promptly occurred in all 27 patients. The acid-base balance returned to normal within three to fourteen days. The urea clearance, as noted previously, returned to original levels in all but 2 patients. However, the restoration of a normal electrolyte equilibrium did not take place as rapidly as it does when alkalis are discontinued in addition to the administration of fluids and sodium chloride.

The following case further demonstrates that, even in severe alkalosis, the addition of sodium chloride to the program may correct the acid-base disturbance despite the continued use of calcium carbonate:

CASE 2 (chart 2).—M. W., a woman aged 68, a housewife, had complained of symptoms of ulcer for eleven years. She had been treated at the University Clinics for nine years, during which time alkalis had been taken periodically. Her blood pressure fluctuated between 198 systolic and 100 diastolic and 210 systolic and 100 diastolic, but renal function (urea clearance and concentration tests) was normal. Prior to entry into the hospital, the patient had vomited repeatedly. Roentgenograms revealed marked pyloric stenosis. Severe alkalosis was noted on the fifth day of therapy. The urine contained occasional hyaline casts; its specific gravity was 1.026. Sodium chloride was added to the program on the sixth day, the alkali being continued. The acid-base balance and renal function returned to normal after ten days of sodium chloride treatment. In the following year the patient showed no evidence of alkalosis despite the continued use of calcium carbonate. The degree of pyloric stenosis lessened, and nightly gastric aspirations now yield only small amounts.

#### COMMENT

The mechanism of the alkalosis described in this series of patients is not entirely clear, although it is probable that more than one factor is involved. As noted previously, antecedent renal damage was not present in the majority of cases. It has been suggested<sup>38</sup> that part of the carbonate ion may be absorbed into the blood, thereby disturbing the acid-base balance. Although the total base values did not exceed normal limits, this possibility must be definitely considered. Cooke has suggested also that insoluble salts may "fix" the gastric juice, thus preventing the normal neutralization of alkaline intestinal secretions and making available for absorption an increased quantity of base. Evidence to confirm or deny these assumptions would be extremely important. The fact that sodium chloride corrected the acid-base imbalance despite continued ingestion of calcium carbonate suggests that we are dealing with primary hypochloremia. There is good reason to believe that the Sippy regimen tends to produce in some patients, at least, a chloride deficiency. Thus the daily intake of sodium chloride by these patients was estimated to be 2.33 Gm., as compared with the average normal intake of 10 to 12 Gm. Chloride depletion is particularly marked in persistent vomiting, as demonstrated in several of the cases. A further source of chloride loss is the aspiration of gastric contents, one of the routine procedures in the Sippy program. In this manner, several hundred milligrams of chloride may be removed daily; this removal, in a patient already on a low chloride intake, may be distinctly detrimental. The loss of chloride by this method is considerably greater in patients with pyloric stenosis and gastric retention.

The quantity of gastric contents removed in the 2 patients described previously averaged from 200 to 400 cc. daily; in the entire group with alkalosis the nightly aspirations exceeded 200 cc. in 17 of the 32 patients. However, it is difficult to explain entirely on this basis the absence of acid-base disturbances in five persons whose aspirations exceeded 200 cc. daily and the occurrence of alkalosis in 2 patients in whom aspiration was not done. Kiefer has attributed the increased frequency of alkalosis, when gastric hypersecretion is present, to the loss of chloride resulting from increased sodium excretion. Another possibility is that calcium carbonate may remove large amounts of chloride from the gastric juice, some of which may not be reabsorbed. Binger and Goldschmidt<sup>39</sup> have shown

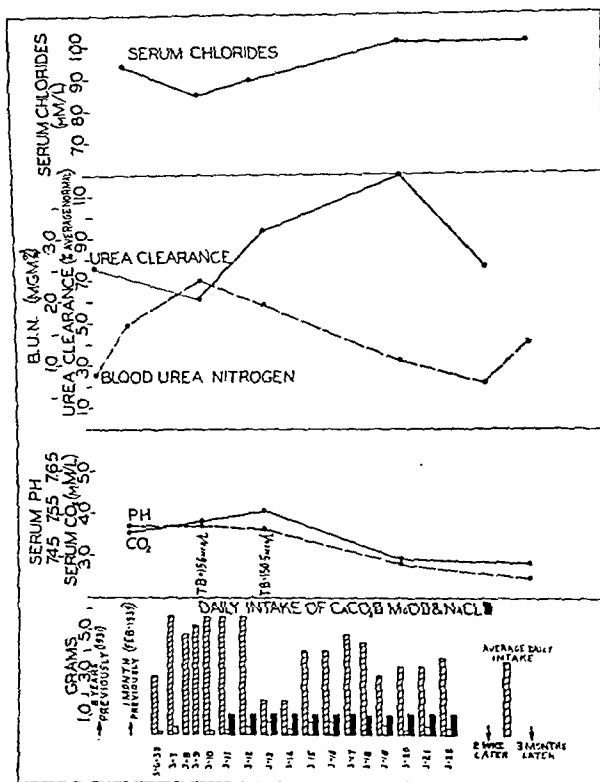


Chart 2.—Effect of sodium chloride and calcium carbonate administration on blood chemistry in case 2.

that calcium lactate in increasing concentration first accelerates, then inhibits the absorption of chlorides from solutions of sodium chloride in the intestine. Studies in progress on this problem<sup>40</sup> indicate that the feces contain larger amounts of chloride after ingestion of calcium carbonate than in control periods, although it is doubtful that this chloride loss is of primary significance. The question of intestinal absorption of chlorides is obviously a complicated problem since, as Lyall<sup>41</sup> pointed out, intestinal secretions contain up to 0.64 per cent of sodium chloride while the chloride concentration of the intestinal contents for absorption is of the same order. It is probable, however, that the loss of chloride is of importance chiefly as a contributory factor, since in 73 patients on a similar

39. Binger, C. A. L., and Goldschmidt, S.: Studies in the Mechanism of Absorption from the Intestine: VI. The Colon; the Influence of Calcium Salts upon the Absorption of NaCl in the Intestine, *Am. J. Physiol.* 48: 473 (May) 1919.

40. Kirsner, J. B.: Unpublished studies.

41. Lyall, Alexander: The Pathology of Chloride Metabolism in Man, *Brit. M. J.* 2: 760 (Oct. 14) 1939.

38. Peters, J. P.: Personal communication to the authors. Cope.<sup>12</sup>

regimen alkalosis did not develop. In 11 of these, however, the serum chloride decreased several millimols during calcium carbonate therapy. The problem may be related to differences in gastric secretion, variations in the salt intake and salt reserve of the body, and varying plasma volumes prior to treatment. In this connection, 1 patient with alkalosis had worked near blast furnaces and, although he perspired profusely, did not take the sodium chloride tablets which were available.

The rapid improvement in renal function after the use of sodium chloride in these patients is of considerable interest. It has been recognized for some time that decreased renal function is a regular concomitant of hypochloremia. Romalo and Dumitresco<sup>42</sup> observed in 1914 that the blood urea nitrogen was higher in nephritis during periods of reduced salt intake than in periods when the diet contained more salt. Chabanier and Lobo-Onell,<sup>43</sup> Host<sup>44</sup> and Landis and his associates<sup>45</sup> have also noted a decrease in renal function during periods of reduced salt intake. These observations were not confirmed by Cope,<sup>46</sup> who apparently produced only a mild chloride deficiency. Many investigators, especially the French,<sup>47</sup> have expressed the belief that the decrease in chlorides directly impairs renal function and is directly responsible for the acute rise in nonprotein nitrogen. This theory has been disputed by Kerpel-Fronius,<sup>48</sup> Clausen<sup>49</sup> and others,<sup>50</sup> who attributed the so-called "azotemia" to a withdrawal of sodium and its sequelae. Extrarenal azotemia, in fact, has been produced experimentally in the absence of hypochloremia.<sup>51</sup> Likewise one of us (J. B. K.) has been able to produce experimentally hypochloremia without azotemia.<sup>52</sup> The volume of extracellular fluids cannot be maintained without normal amounts of sodium and chloride; consequently, the loss of these ions is invariably accompanied by a decrease in the extracellular fluid, or dehydration.<sup>53</sup> McCance<sup>54</sup> has actually found a reduction of 28 to 38 per cent in the volume of body fluids in experimental human salt deficiency. Although measurements of the fluid balance in 4 out of 6 of our patients did not reveal any significant changes in the urinary output prior to and during alkalosis (the fluid intake and output increased somewhat after the addition of sodium chloride) dehy-

dration may well have been present in these patients. Indeed, dehydration may occur even though the total body water remains unchanged, for the intracellular content of fluid may be increased at the expense of the extracellular fluid.<sup>55</sup> Renal function is usually decreased in dehydration.<sup>53</sup> McCance and Widdowson have observed a fall in the creatinine, sucrose, inulin and urea clearances in experimental salt deficiency. The lowered renal efficiency has been attributed to a reduction in the rate of glomerular filtration, which may itself result from a combination of factors. These include increased colloidal osmotic pressure of the blood, decreased blood volume, increased blood viscosity, a reduction in the number of "active" glomeruli (due to the decreased blood volume) and a decreased rate of circulation.<sup>56</sup> In fact, Gömöri and his co-workers<sup>57</sup> have demonstrated a reduction in the rate of circulation and a decrease in filtration pressure under similar conditions. The lowered urea clearances described in the present study suggest that renal failure was due either to a decreased renal blood flow or to a less complete extraction of urea from the blood. Since the renal tubules function best when the serum concentration of electrolytes is normal,<sup>58</sup> it is possible also that decreased tubular efficiency may be responsible in part for some of the changes. The importance of dehydration is further indicated by the fact that severe acute alkalosis may be produced experimentally without impairment of urea and creatinine clearances when care is taken to avoid depletion of fluid.<sup>59</sup> The elevated blood urea nitrogen does not necessarily indicate renal failure in the pathologic sense;<sup>60</sup> it is due to the decreased renal function and perhaps to increased tissue catabolism during dehydration.<sup>61</sup>

The beneficial effect of sodium chloride on renal function in the patients discussed is an indirect one and seems to be related entirely to the correction of dehydration. Thus, sodium chloride makes it possible to increase the volume of extracellular fluids by extracting water from the cells and by increasing the intake of fluids.

The augmented plasma volume, as Gömöri,<sup>57</sup> Berenson<sup>62</sup> and others<sup>63</sup> have shown, improves renal function by increasing the rate of circulation and the rate of glomerular filtration.

#### SUMMARY AND CONCLUSIONS

Alkalosis developed in 32 of 105 patients who received calcium carbonate in the treatment of peptic ulcer. The tendency to alkalosis was not related to

42. Romalo, E., and Dumitresco: Administration du chlorure de sodium aux néphrétiques, chlorurémiques et azotémiques, *Compt. rend. Soc. de biol.* **76**: 676, 1914.

43. Chabanier, H., and Lobo-Onell, C.: Hypochlorémie et accidents postopératoires, Paris, Masson & Cie, 1934; cited by Chabanier, H., Lobo-Onell, C.; Lieutaud, P., and Lelu, E.: Poussée Aiguë d'hyperazotémie, *Presse méd.* **42**: 844 (May 23) 1934.

44. Host, H. F.: On Chloride Metabolism, *J. Lab. & Clin. Med.* **3**: 713, 1918.

45. Landis, E. M.; Elsom, K. A.; Bott, P. A., and Shiels, E.: Observations on Sodium Chloride Restriction and Urea Clearance in Renal Insufficiency, *J. Clin. Investigation* **14**: 525 (Sept.) 1935.

46. Cope, C. L.: Studies of Urea Excretion: VIII. The Effects on the Urea Clearance of Changes in Protein and Salt Contents of the Diet, *J. Clin. Investigation* **12**: 567 (May) 1933.

47. Blum, L.; Grabar, P., and Van Cauelaert, C.: L'azotémie par manque de sel, *Press. méd.* **36**: 1411 (Nov. 7) 1928; l'azotémie par manque de sel, son mécanisme, *Ann. de méd.* **25**: 34 (Jan.) 1929.

48. Kerpel-Fronius, E.: Zur Pathogenese der "hypochlorämischen" Azotämie, *Ztschr. f. d. ges. exper. Med.* **97**: 733, 1936.

49. Clausen, J.: Studies on the Relation Between Hyperazotemia and NaCl Deficiency, *Acta med. Scandinav.* **91**: 523, 1937.

50. Gömöri, P., and Frenreisz, S.: Influencing Hypochloremic Azotemias with Hypertonic and Physiological NaCl Solutions, *Acta med. Scandinav.* **92**: 503, 1937.

51. Kerpel-Fronius, E.: Salz-mangelzustände und chloroprive Azotämie, *Ergebn. d. inn. Med. u. Kinderh.* **51**: 623, 1936.

52. Kirsner, J. B.: The Production of Hypochloremia Without Azotemia, to be published.

53. Gamble, J. L.: Dehydration, *New England J. Med.* **201**: 909 (Nov. 7) 1929; Extracellular Fluid, *Bull. Johns Hopkins Hosp.* **61**: 174 (Sept.) 1937.

54. McCance, R. A.: The Effect of Salt Deficiency in Man on the Volume of the Extracellular Fluids and on Composition of Sweat, Saliva, Gastric Juice, and Cerebro-spinal Fluid, *J. Physiol.* **92**: 208 (March 14) 1938.

55. McCance, R. A.: Experimental Sodium Chloride Deficiency in Man, *Proc. Roy. Soc., London, S.B* **119**: 245, 1932. Darrow, D. C., and Yannet, Herman: Metabolic Studies of the Changes in Body Electrolytes and Distributions of Body Water Induced Experimentally by Deficit of Extracellular Electrolyte, *J. Clin. Investigation* **15**: 419 (July) 1936.

56. Fishberg, A. M.: Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1934, p. 40. Gömöri, Podhradzsky and Kring,<sup>57</sup> McCance and Widdowson,<sup>57</sup> Clausen.<sup>49</sup>

57. Gömöri, P.; Podhradzsky, L., and Kring, J.: The Significance of Circulation in the Pathogenesis of Extrarenal Azotemias, *Acta med. Scandinav.* **102**: 591, 1939.

58. Darrow, D. C.: The Treatment of Dehydration, Acidosis and Alkalosis, *J. A. M. A.* **114**: 655 (Feb. 24) 1940. Nicol.<sup>59</sup>

59. Kirsner, J. B., and Alpert, L. K.: The Urea and Creatinine Clearance in Experimental Acute Alkalosis, to be published.

60. MacKay, L. L., and MacKay, E. M.: Increased Blood Urea Concentration of Extrarenal Origin, *Am. J. Physiol.* **70**: 394 (Oct.) 1924.

61. Straub: *Ztschr. f. Biol.* **37**: 527, 1899; **38**: 538, 1899; cited by MacKay.<sup>60</sup>

62. Berenson, J.: L'influence de diurétiques et du chlorure de sodium sur la filtration et l'absorption rétrograde dans les reins, *compt. rend. Soc. de biol.* **121**: 1553, 1936.

63. Gollwitzer-Meier, K.: Die hämodynamische Wirkung akuter Veränderungen der Blutmenge bei verschiedener Gefäßreaktion, *Arch. f. d. ges. Physiol.* **218**: 586, 1928. Mészáros, Karl: Die Wirkung hypertensischer Lösungen auf die Capillaren, *Ztschr. f. klin. Med.* **122**: 316, 1932.



the quantity of calcium carbonate prescribed. Symptoms usually appeared within three to eight days after the onset of treatment and consisted of a distaste for milk and cream, excessive dryness of the mouth and throat, anorexia, dizziness, headache, nausea and vomiting. There was no correlation between the severity of symptoms and the degree of chemical alkalosis. The carbon dioxide combining power and  $p_H$  were elevated and the serum chlorides were markedly lowered during alkalosis. The total base in 12 patients with a normal acid-base balance and in 8 patients with alkalosis did not exceed normal values. The serum calcium was not elevated except in 1 patient. Neither anemia nor hepatic disease was of etiologic significance. The urea clearance was normal in 22 of 32 patients prior to the onset of alkalosis. Twelve patients with reduced urea clearances did not show any acid-base disturbance. The urea clearance decreased in 25 patients during alkalosis. In 9 cases the clearances fell below 20 per cent of average normal. The blood urea nitrogen rose concomitantly, reaching a peak of 67.6 mg. per hundred cubic centimeters in 1 case. In 2 patients the urine during alkalosis contained traces of albumin. In a third case, the urine was acid and contained albumin, casts and red blood cells. Renal function returned to original levels in 23 of the 25 patients within seven to fourteen days after the onset of treatment. In 3 cases recovery occurred only after one, three and six months had elapsed.

A total of 27 patients with alkalosis during the administration of calcium carbonate were treated by the addition of sodium chloride, the alkali being continued. Clinical improvement was prompt in all cases and, despite the continued use of calcium carbonate, the acid-base balance returned to normal within seven to fourteen days. The mechanism of the alkalosis following the administration of calcium carbonate has not been conclusively established. Chloride deficiency seems to be the most important factor although absorption of carbonate ions may play a role. Hypochloremia may be due to (a) low intake of sodium chloride, (b) loss of chloride from vomiting or from the aspiration of the gastric contents and (c) increased excretion of chloride in the feces. However, other factors as yet unknown are involved since, in this series, alkalosis did not develop in 73 patients on a similar regimen. The reduced renal function is probably due to dehydration with consequent decrease in the rate of glomerular filtration. The beneficial effect of sodium chloride on the acid-base balance and on renal function, despite the continued use of calcium carbonate, is due to the correction of hypochloremia and to the establishment of a normal water balance.

Alkalosis after the administration of calcium carbonate is primarily due to a deficiency of chloride and to consequent dehydration. The alkalosis may be combated successfully by the administration of adequate quantities of sodium chloride and fluid even though the ingestion of calcium carbonate is continued. However, the most effective means of treating alkalosis still remains the discontinuance of alkali in addition to the administration of adequate amounts of sodium chloride and fluid.

Renal function, as measured by the urea clearance test, is usually markedly depressed during alkalosis but returns to its previous level after the electrolyte balance is restored.

## ABSTRACT OF DISCUSSION

DR. DANA W. ATCHLEY, New York: Clinically it is worth while to point out the incorrectness of the common concept that calcium carbonate is an inert substance and may be used as effective alkali without disturbing the acid-base equilibrium. That concept is a common one. I was not clearly aware of it. One of the reasons that we haven't noticed much of this is that in New York, at least at the Presbyterian Hospital, we are not quite so enthusiastic about the use of alkalis. We treat many cases of ulcer with diet alone and without the introduction of alkali or drainage (never with gastric drainage). The clinical picture described is not one that is associated with the other types of alkalosis with which one is familiar. It is a picture that could well be associated with dehydration, and I should like to ask the authors whether, during the course of their observation of these patients, they carried out any sequential determination of hemoglobin or serum protein percentage or daily weights which would give some index as to whether or not there had occurred a dehydration sufficient to produce the renal effects that they observed or sufficient to produce the clinical picture. Such findings, if present, would explain the therapeutic benefit of sodium chloride. I want to express my appreciation of the instructive nature of this clinical contribution. When I come to the chemical side I hardly know where to begin. Too many of my treasured concepts have been overthrown. The degree of alkalosis from purely a point of view of the  $p_H$  of the circulating plasma is amazing. The authors present figures with which I am not familiar and which are extraordinary in the degree, quantitatively, with which this alkalosis has actually disturbed the hydrogen ion concentration. This is a tremendous upset toward the alkaline side. It is difficult to understand this effect of calcium carbonate. Calcium chloride is a diuretic which I have always felt acted because it produced an acidosis, a genuine acidosis with loss of carbon dioxide and a true change of  $p_H$  to the acid direction. I assumed that that was due to the fact that calcium formed insoluble salts and was removed, excreted entirely or almost entirely by the intestinal tract, in that way freeing the chlorine to act as an acid ion. If that is true, one would expect an analogous disturbance with calcium carbonate, although carbonic acid is a much weaker acid than hydrochloric acid.

DR. L. C. GATEWOOD, Chicago: When Haden and Orr first showed that the intravenous or subcutaneous use of sodium chloride would correct alkalosis I began that treatment when alkalosis occurred in the course of ulcer management, particularly when associated with obstruction. It was manifest that, if the patient was not vomiting, the intake of chloride by mouth should have the same effect as the intravenous or subcutaneous use. As long as ten years ago I used the same technic which Drs. Kirsner and Palmer described, giving sodium chloride by mouth in doses of 5 to 10 Gm. a day and have verified what he has reported. There are some interesting sidelights on this which bear on the question of alkalosis and other body chemistry. It is related probably to a depletion of chlorides from the body, and in just what way I do not think has been determined. In the treatment of a patient with duodenal ulcer and pyloric obstruction, alkalosis developed. Hydrochloric acid secretion in the stomach promptly disappeared. Alkali was stopped and chloride was given to correct the alkalosis. There was no immediate return of hydrochloric acid secretion, although acid-base equilibrium was promptly brought back to normal, and the patient continued without hydrochloric acid secretion for a period of three months. Then secretion gradually returned to normal. After a time she was again given a few doses of alkali (calcium carbonate and sodium bicarbonate) and promptly her hydrochloric acid again disappeared and a slight degree of alkalosis recurred, immediately corrected with sodium chloride. I have made similar observations on a number of occasions. The exact demonstration of the chemistry involved in this is not at all simple, because it requires some means of determining chlorides other than the blood chloride. The blood chlorides on this regimen could be kept at about normal levels, so in order to solve the problem it is necessary to determine rather completely all the body losses of chloride and also to make some

determinations of tissue chloride. It is suggested that possibly determination of spinal fluid chloride might yield some light on this in the same way that determinations of calcium content in the spinal fluid and comparison of those with the blood calcium shed light on calcium storage a number of years ago.

DR. E. N. COLLINS, Cleveland: The work of Haden and Orr has been mentioned. Naturally association for a number of years with Dr. Haden at the Cleveland Clinic has made me "chloride conscious." Urinary chloride determinations have proved significant in the treatment of alkalosis. In our experience these determinations give more accurate values relative to the acid-base balance of the patient than the blood chloride determinations. General practitioners who do not have a blood chemistry laboratory at their disposal can easily make those determinations. In patients who have pyloric obstruction, in addition to giving the usual parenteral therapy to overcome dehydration I routinely give a 3 per cent solution of hypertonic sodium chloride intravenously, usually 500 cc. in 5 per cent dextrose solution once or twice during the twenty-four hour period. The solution is given very slowly and is checked by daily determinations of the urinary chloride. An attempt is made to keep the urinary chlorides above 5 Gm. in twenty-four hours. When or if the obstruction is relieved, sodium chloride is given by mouth if the urinary chloride determinations do not show normal findings by that time. One feature about the presentation of Drs. Kirsner and Palmer that surprises me is the length of time it takes to bring these patients back to a normal acid-base balance. In my experience giving hypertonic saline solution intravenously in cases in which there is obstruction for three or four days suffices.

DR. JOSEPH B. KIRSNER, Chicago: We also were puzzled by the chemistry of calcium carbonate when this first became known to us, and through correspondence with various men in the East we learned that others also were puzzled. The question of dehydration is of paramount importance. We are undertaking a study to settle that question. I might cite from the literature, however, McCann's work demonstrating in alkalosis a reduction in the volume of extracellular fluid of approximately 28 to 38 per cent. We have determined the hemoglobin frequently and have not been impressed by any marked changes. I have not tabulated the daily weights, although we have those data available. As far as the  $p_{\text{H}}$  being too high is concerned, I should point out that the  $p_{\text{H}}$  of 7.73 was only one observation of many; in our laboratory we are inclined to place less reliance on the  $p_{\text{H}}$  than any other feature of the acid-base balance, because as a colorimetric method it is subject to many technical errors. The question of the absorption of calcium carbonate is extremely interesting. We have been carrying out metabolic studies on this point and I can say positively at this time that after the administration of calcium carbonate the urinary calcium increases from two to five times that in the precalcium carbonate period. The explanation is not yet apparent. I should like to point out that Dr. Gatewood was among the first to indicate the relation between hypochloremia and alkalosis, and we have drawn on his writings frequently. In other experiments we have been able to reduce the chlorides in animals from 115 millimols per liter to 38, determining the  $p_{\text{H}}$  of the gastric juice and the total chlorides, and have found no significant variation. This observation has also been made previously by other workers. The difficulty of giving sodium chloride in large enough amounts has been an individual problem. We found certain patients in whom 5 Gm. was not enough and we have had to increase the amount to 10 Gm. daily; the second patient required about 20 Gm. The question of spinal fluid chloride is important. In two cases of alkalosis reported in the *Lancet* the spinal fluid chlorides were found to be reduced in a measure similar to that found in the blood. Dr. Gatewood's suggestion about chlorides other than blood chlorides is another matter which we intend to look into. In our group of patients with alkalosis there were some whom we might classify as having pyloric stenosis, but I should like to make it clear that the majority did not have pyloric stenosis. As to the length of time for the return to normal of the electrolyte balance, of course, when one gives sodium chloride intravenously the return to the acid-base balance will take place in several days.

## SEQUELAE OF SEVERE DISEASE OF THE ABDOMINAL VISCERA

WITH SPECIAL REFERENCE TO PSYCHONEUROSIS AND  
IMBALANCE OF THE AUTONOMIC  
NERVOUS SYSTEM

A. R. VONDERAHE, M.D.

CINCINNATI

It is my purpose in this paper to inquire into a group of cases of psychoneurosis whose origins date to an attack of irritative disease of the abdominal viscera of such severity as to have been associated with the probability of imminent death, or which are associated with diseases of the abdominal viscera characterized by a chronic course of increasing severity. In this group are cases of peptic ulcer with massive hemorrhage, ruptured peptic ulcer, surgical intervention in peptic ulcer with extremely stormy postoperative course, severe typhoid with delirium, carcinoma of the gastrointestinal tract, cases of poisoning by mouth with associated gastroenteritis and similar diseases having in common the factors of irritation and of extreme gravity of outcome in some part of their course.

These conditions are met in the course of neuro-psychiatric practice and are variously diagnosed as psychoneurosis, neurasthenia, autonomic imbalance or neurocirculatory asthenia. In the more severe form there is such quick development of exhaustion that the normal occupation cannot be pursued at all or in any event is greatly restricted. The patient gives the impression of still being in a convalescent period long after the acute illness is over.

Subjectively, there are feelings of inadequacy associated with apprehension and mild depression. There are complaints of awareness of the heart beat, breathlessness after slight exertion or excitement and quick development of fatigue on slight exertion. On physical examination there are an irritable pulse rate, vasomotor changes in the hands and feet, myotatic irritability, hyperactive muscular reflexes, increased axillary perspiration, low blood pressure, occasionally subnormal temperature or alterations of the normal temperature rhythm. With laboratory studies there may be found a lowered basal metabolic rate and abnormal blood sugar tolerance curves with a tendency to hypoglycemic reaction.

### RELATIONSHIP OF PATHOLOGIC ALTERATIONS IN THE CENTRAL NERVOUS SYSTEM TO SYMPTOMS

The evidence for organic changes in the central nervous system accompanying diseases of the abdominal viscera may be considered in two phases: first, pathologic alterations accompanying the acute phase of the visceral disease and secondly, the healing of such pathologic alterations with resultant scarring and consequent disturbances of function.

In 1881, Wernicke<sup>1</sup> gave an extremely lucid account of the symptoms, signs, clinical course and autopsy in 3 patients who presented in common punctate hemorrhage in the walls and floor of the third ventricle, the massa intermedia of the thalamus and occasionally

<sup>1</sup>From the Department of Anatomy (Neurology), University of Cincinnati College of Medicine.

Read before the Section on Nervous and Mental Diseases at the Ninety-First Annual Session of the American Medical Association, New York, June 12, 1940.

1. Wernicke, Carl: *Lehrbuch der Gehirnkrankheiten für Aerzte und Studierende*, Berlin, Theodor Fischer, 1881, p. 229-242.

the gray matter of the aqueduct of Sylvius and of the fourth ventricle. He summarized the characteristic clinical manifestations as follows: (1) disturbance of consciousness, (2) somnolence or agitation followed by somnolence, (3) reeling gait, (4) partial to complete paralysis of the eye muscles and (5) inflammatory (hemorrhagic) changes in the retina.

Wernicke's first case was that of a 20 year old seamstress who had taken sulfuric acid by mouth. No history of alcoholism was noted. The characteristic signs appeared, and the illness ran a course of forty-one days. At autopsy there was noted a stenosis of the pylorus, gastrectasis and chronic ulceration of the stomach. In the walls of the third ventricle there were numerous small hemorrhages distributed on both sides. Similar hemorrhages occurred in the massa intermedia of the thalamus. In this case hemorrhages were not noted in the corpora quadrigemina of the mid-brain or in the cerebellum, but the hemorrhages occurred in the retina. Wernicke designated the neuropathologic diagnosis "Encephalitis haemorrhagica substantiae griseae ventricul. III."

The other 2 cases of Wernicke were associated with alcoholic psychosis (delirium tremens). In both cases hemorrhages occurred in the hypothalamus as well as in the gray matter of the aqueduct of Sylvius and in the floor of the fourth ventricle, especially localized in the calamus scriptorius. It is noteworthy that Wernicke did not in any way limit the disease to association with severe alcoholism, although in subsequent years the error was made and some authors specifically limited the term first used by Wernicke, "acute hemorrhagic polioencephalitis superior," to those cases occurring with alcoholism. It appears clear from Wernicke's description that he attempted to build a clinical entity, based on hemorrhagic findings in the brain stem, entirely analogous to that occurring in the spinal cord in acute anterior poliomyelitis. For this reason, apparently, he emphasized the findings in the somatic motor nuclei (especially those to the eye muscles) whereas these are not at all constant even in the alcoholic form, while somnolence, alterations of consciousness and emotion are invariably present. Acute anterior poliomyelitis became a disease ascribable to an infectious agent while acute hemorrhagic polioencephalitis superior remains a pathologic complex occurring with many different conditions; for this reason it is desirable to use some such term as Wernicke's encephalopathy<sup>2</sup> to designate the characteristic pathologic findings.

**Acute Encephalopathy.**—In every one of 14 patients with peptic ulcer who came to autopsy, hemorrhages in the anterior hypothalamus, massa intermedia and the medial wall of the dorsal thalamus have been observed. In 7 of the cases in which the medulla was examined, hemorrhage was noted also in the dorsal motor nucleus of the vagus. An alcoholic history was prominent in only 2 of the cases. Nine of the cases were associated with perforation of the ulcer and peritonitis. 2 cases with continuous slow bleeding, 2 cases with bronchopneumonia after gastroenterostomy and 1 with massive hemorrhage into the gastrointestinal tract. Two of the cases were associated in their terminal stage with hyperglycemia and glycosuria.<sup>3</sup>

Somewhat similar hemorrhages were found in other cases of irritative disease of the abdominal viscera: tuberculous peritonitis, typhoid, carcinoma of the cervix uteri with fistula into the bladder and rectum, and poisoning with saponated solution of cresol. In a series of cases of carcinoma of the stomach recent and

healed hemorrhages were also found. In a group of 20 control cases which included instances of cardiac failure, carcinoma of the lung, malignant hypertension, Addison's disease and acute bacterial endocarditis, hemorrhagic changes were not noted. Of 20 cases of diabetes mellitus, hemorrhages in the hypothalamus occurred in 9.

The following case, briefly summarized, will serve as an illustration of the foregoing discussion:

**CASE 1.—Chronic duodenal ulcer; perforation; peritonitis.**

A white man aged 59 presented complaints over a period of three years of indigestion and frequent attacks of pain after eating. He was not addicted to alcohol. There was a sudden attack of severe cramping pain in the abdomen, and the patient was transferred to the Hamilton County Chronic Disease Hospital on the following day, at which time he was already desperately ill. The abdominal muscles were rigid. The temperature was 102.5 F. There was repeated vomiting. The heart presented extrasystoles. The pulse rate, which was 128 on entrance to the hospital, became progressively more rapid, so that counting was impossible. The patient died the day after entrance into the hospital.

On autopsy there was found a perforated duodenal ulcer and acute generalized fibrinopurulent peritonitis. Serial sections



Fig. 1 (case 1).—Multiple hemorrhages are present in the oral portion of the dorsal motor nucleus of the vagus nerve. Involved in the hemorrhages are preganglionic neuron cell bodies to the stomach and duodenum and cell bodies of the nucleus cardiacus (Malone). Morgan's stain. Slightly reduced from a photomicrograph with a magnification of 16 diameters.

of the entire brain stem and diencephalon as well as several cortical areas, after staining and microscopic study, revealed multiple hemorrhages limited to the following structures: (1) oral portion of the dorsal motor nucleus of the vagus (fig. 1), (2) superior and anterior portion of the hypothalamus at the level of the nucleus paraventricularis, especially in the region between the fornix and the hypothalamic sulcus and (3) the massa intermedia of the thalamus involving cells of the nucleus paramedianus and nucleus reuniens complex. There were no hemorrhages in the corpora quadrigemina, the mamillary bodies of the nuclei of the third, fourth and sixth cranial nerves.

The tendency of hemorrhages of the Wernicke type to occur with diseases of the gastrointestinal tract is well substantiated from the literature. Wernicke's<sup>1</sup> first case, ulceration of the stomach associated with sulfuric acid poisoning, has been noted. Roemer<sup>4</sup> called attention to the role of botulism developing in the course of ptomaine poisoning by meat, sausage, fish and oysters and accompanied clinically by paralysis

2. Campbell, A. C. P., and Biggart, J. H.: Wernicke's Encephalopathy (Polioencephalitis Haemorrhagica Superior): Its Alcoholic and Non-alcoholic Incidence, *J. Path. & Bact.* 48: 245-262 (March) 1939.

3. Vonderahe, A. R.: Histopathologic Changes in the Nervous System in Cases of Peptic Ulcer, *Arch. Neurol. & Psychiat.* 41: 871-912 (May) 1939.

4. Roemer, Paul: *Textbook of Ophthalmology in the Form of Clinical Lectures*, translated by M. L. Foster, New York, Reiman Company, 1913, pp. 611-613.

of the eye muscles and other cerebral manifestations. Sträussler<sup>5</sup> described 2 cases occurring during the course of obstruction of the bowel. Harmes<sup>6</sup> in a discussion of alcoholic forms of Wernicke's encephalitis noted the frequent occurrence of chronic gastritis in these cases and suggested that some form of gastro-intestinal intoxication may be an important factor. The characteristic pathologic findings have also been noted in puerperal fever, bilateral sarcoma of the kidneys and typhoid.<sup>7</sup> Campbell and Biggart<sup>2</sup> reported 12 cases of Wernicke's encephalopathy, of which 3 were associated with gastric carcinoma, 1 with an old gastroenterostomy, 2 with hyperemesis gravidarum and one with chronic pyosalpinx. These findings, of course, do not exclude the fact that hemorrhagic phenomena have been observed in some other conditions—vitamin B<sub>1</sub> deficiency,<sup>8</sup> hypochloremia,<sup>9</sup> fatal ether anesthesia<sup>10</sup> and, as noted previously, in occasional cases of diabetic acidosis.

*Subacute and Chronic Encephalopathy.*—Clinically, it is known that people suffering from visceral abdominal disease of such gravity as to present some of the

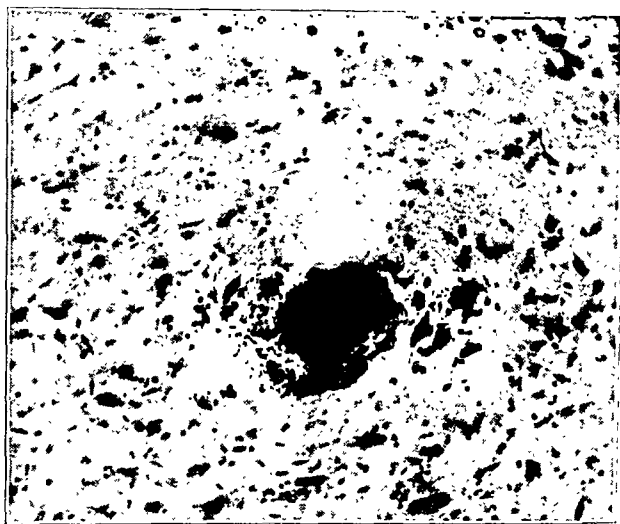


Fig. 2 (case 2).—An older hemorrhage is present in the anterior hypothalamus. There are present some degeneration of red blood cells, deposits of pigment and an area of parenchymatous degeneration. Morgan's stain. Reduced from a photomicrograph with a magnification of 130 diameters.

signs of Wernicke's encephalopathy sometimes recover. In the alcoholic form recovery occurs occasionally but not completely, a defect in the psychic sphere tending to persist.<sup>6</sup> These observations are borne out by demonstrable anatomic changes.

In the 14 cases of peptic ulcer noted previously, 4 patients with chronic gastric ulcer and 1 with gastric ulcer with malignant change (adenocarcinoma) presented in the anterior hypothalamus partly disintegrated red blood cells and evidence of glial proliferation. In 2 of the aforementioned cases glial proliferation and particles of pigment were also noted in the oral part of

the dorsal motor nucleus of the vagus. In a series of cases of carcinoma of the stomach there occurred in the hypothalamus, in association with more recent hemorrhagic changes, areas of pale-staining red blood cells, disintegrated red blood cells and occasionally evidence of glial replacement.

These observations may be illustrated in the following case:

**CASE 2.—History.**—A white woman aged 59 was a resident with her sister, of the Hamilton County Home. For approximately six months prior to her death there was noted a loss of weight and an increasing amount of weakness, so that the patient required to be constantly helped by her sister. She was not, however, given to complaining, and aside from the progressive exhaustion there were few or no subjective symptoms. She was taken suddenly ill with an attack of severe nausea and vomiting and was transferred on the following day to the Hamilton County Chronic Disease Hospital.

**Physical Examination.**—On admission the pulse rate was 120, the respiratory rate was 30 and the blood pressure was 80 systolic and 50 diastolic. Examination of the abdomen revealed some rigidity and a questionable mass in the epigastrium. There was continuous vomiting. Six hours after admission the patient showed a decided change for the worse. The pulse rate dropped to 60. There was mental confusion and delirium. Six hours later the pulse rate was barely perceptible and the heart sounds were scarcely audible. The pulse continued to be slow and scarcely perceptible until death.

**Postmortem Examination.**—The autopsy revealed coronary sclerosis with acute myocardial infarction, which was regarded as the primary cause of death. In addition there was found a deep ulcer on the inferior wall of the stomach with thickened and indurated margins involving the mucous membrane of the body of the stomach above the pylorus. Microscopic sections through this area revealed that, in addition to the ulcer, malignant changes (adenocarcinoma) were present. Examination of serial sections through the diencephalon revealed small hemorrhages in the hypothalamus at the level of the paraventricular nucleus. The hemorrhages extended caudally to implicate the cells of the nucleus reuniens complex in the massa intermedia, together with the nucleus paramedianus of the thalamus. In addition to these fresh hemorrhages, older hemorrhages were found in the hypothalamus close to the hypothalamic sulcus. The old hemorrhages were characterized by disintegrated red blood cells, deposits of iron pigment (staining characteristically with Turnbull's blue and prussian blue) and local degeneration of the parenchyma (fig. 2). There was only slight phagocytic reaction. However, there were areas of patchy, intense gliosis (fig. 3) surrounding blood vessels, especially in the preoptic region of the thalamus.

**Comment.**—This case, in its pathologic aspects, presents evidence of hemorrhagic phenomena apparently occurring at different intervals of time. The case is of especial interest because death from myocardial infarction occurred suddenly.

Neubürger<sup>11</sup> presented evidence of healing of the hemorrhages characteristic of Wernicke's encephalopathy in its nonalcoholic forms. The author studied the hypothalamus and brain stem in 6 cases of carcinoma of the stomach, 1 of carcinoma of the head of the pancreas, 1 of sarcoma involving the liver and mucosa of the stomach and 1 of chronic atrophic gastritis. In addition to fresh hemorrhage, Neubürger found frequent evidence of perivascular blood casts and glial replacement, proliferated blood vessels with small areas of degeneration and areas of blood pigment around the blood vessels. His observations were amplified in a subsequent study of the central nervous system in chronic gastritis.<sup>12</sup> In alcoholic forms, Bender and

5. Sträussler, cited by Harmes,<sup>6</sup> p. 10.

6. Harmes, Theodor: Klinischer und anatomischer Beitrag zur Lehre von der Poliencephalitis acuta hämorrhagica superior, Neumünster, Germany, R. Hieronymus, 1911.

7. Claude, Henri, and Lévy-Valensi: Maladies du cerveau et de l'isthme de l'encéphale, Paris, J. B. Baillière et fils, 1922, p. 299.

8. Alexander, Leo: Wernicke's Disease: Identity of Lesions Produced Experimentally by B<sub>1</sub> Avitaminosis in Pigeons with Hemorrhagic Poliencephalitis Occurring in Chronic Alcoholism in Man, Am. J. Path. 16: 61-70 (Jan.) 1940.

9. Larson, C. P.: Fatal Cases of Acute Manic-Depressive Psychosis, Am. J. Psychiat. 95: 971-982 (Jan.) 1939.

10. Uchimura, Yushi: Clinical and Pathologic Studies of the Diencephalon, Psychiat. et neurol. jap. 40: 55-57 (Oct.) 1936; abstracted, Arch. Neurol. & Psychiat. 39: 164 (Jan.) 1938.

11. Neubürger, Karl: Ueber die nichtalkoholische Wernickesche Krankheit, insbesondere über ihr Vorkommen beim Krebsleiden, Virchows Arch. f. path. Anat. 208: 68-86, 1936.

12. Neubürger, Karl: Wernickesche Krankheit bei chronischer Gastritis. Ein Beitrag zu den Beziehungen zwischen Magen und Gehirn, Ztschr. f. d. ges. Neurol. u. Psychiat. 160: 208-225, 1937.

Schilder<sup>13</sup> presented numerous instances of reaction to hemorrhage with phenomenon of healing. They pointed out significantly (p. 1048) that the vascular lesions have in general the same distribution as the glial ones but invade more deeply. They also pointed out the presence of capillary budding and proliferative changes in the blood vessels involving both the endothelial and adventitial layers but noted that the absence of inflammatory response is remarkable. They emphasized the electivity of the lesions for vegetative gray masses along the ventricles.

#### PROGNOSIS AND TREATMENT

While the phenomena of hemorrhage are associated with severity and gravity of the clinical course and many of the patients die, there is evidence, pathologically, of progressive stages of healing of the acute lesions and, clinically, that some patients survive. It is not remarkable that among those who survive there should be some who present the residual effects of injury to central autonomic centers. Peptic ulcer has been more completely studied with respect to end results than any other form of abdominal visceral disease. That a diminution of working capacity may occur after severe peptic ulcer has been noted by Meyer and Scher.<sup>14</sup> In a study of the results in 500 cases of ruptured peptic ulcer by Thompson,<sup>15</sup> 51 patients were followed from three to fifteen years; complete relief was obtained after operation in 38.7 per cent and incomplete relief in 61.2 per cent; some type of subsequent therapeutic care was required in all but 12 cases; inability to work for varying periods after operation was experienced in 42.8 per cent. In 2 patients of the group total disability was present.

The treatment of sequelae of severe irritative disease of the abdominal viscera is based on pathologic considerations. The psychotherapy depends on the recognition of an organic handicap traceable to lesions in the central autonomic centers. With this in mind the patient is asked to face the reality of a disability. Since many of the patients are suffering from a depression based on unsuccessful efforts at maintaining too high a level of mental and physical exertion, the resolution of the mental conflict is usually accomplished without difficulty. The irritable pulse rate and respiratory rate require increased physical rest. The metabolic and autonomic symptoms such as hypoglycemic episodes and hypochlorhydria are readily treated symptomatically. Inasmuch as Leo Alexander<sup>8</sup> has shown the similarity of the hemorrhagic lesions in these cases to those produced by B<sub>1</sub> avitaminosis, thiamine hydrochloride is administered in liberal quantities. As a prophylactic measure administration of thiamine hydrochloride for a period of time before the abdominal operation is suggested.

The following clinical case report illustrates the application of some of the foregoing observations:

**CASE 3.—History.**—An unmarried white woman aged 38 complained of pronounced exhaustion and anxiety. There was a mild depression based on the belief that she was lacking in character and will power because she was unable to continue teaching a two hour class in sewing. She also complained of

palpitation and breathlessness after slight exertion, excessive perspiration, occasional dull headaches and pronounced sleeplessness.

She was in good health until the onset of acute ruptured appendicitis at the age of 20. There was an extremely stormy postoperative period, requiring hospitalization for six weeks. At the age of 22 a resection for bowel obstruction was performed. At the age of 24 a gastroenterostomy was done for hemorrhage from a gastric ulcer; the postoperative period again was extremely stormy with a hospital stay of seven weeks. There was blurring of vision for several months. After six months of convalescence the patient attempted to work as a teacher, but the distress and fatigue were so great that she required rest for long periods in order to go on. The patient dated her present difficulties in large part to this illness.

At the age of 28 there developed in the patient excessive menstrual bleeding, and a hysterectomy was done. She again was dangerously ill; however, after repeated transfusions and other restorative measures, she recovered from the immediate operative effects although she remained in the hospital for three

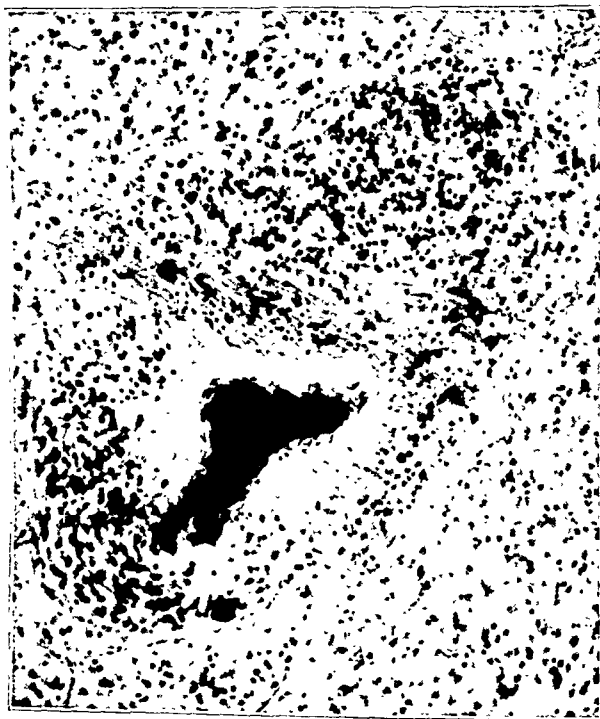


Fig. 3 (case 2).—An area of intense perivascular gliosis is present in the preoptic region of the hypothalamus. Morgan's stain. Reduced from a photomicrograph with a magnification of 130 diameters.

months in a state of invalidism. At the age of 35, because of various gastrointestinal complaints, an exploratory laparotomy was done and the gallbladder was removed; although local anesthesia was used there was extreme shock after the operation, and for several days death was regarded as imminent. The following year, a diagnosis of hyperthyroidism was made and a thyroidectomy was done under local anesthesia; immediately after this operation the patient suffered a psychosis characterized by excitement, excessive psychomotor activity and terror; restraint was required for several days, after which the psychotic manifestations subsided. The patient remained a semi-invalid thereafter, but some improvement occurred with complete rest. After approximately a year, however, having been told "to fight it through" and "to use will power," she attempted to return to her work teaching sewing to children. After three months characterized by progressive emotional and physical disability she presented herself for examination and treatment.

**Physical Examination.**—The patient presented an anxious, depressed appearance. She weighed 98 pounds (44.5 Kg.). The pulse rate, which was 68 in a recumbent position, rose to 90

13. Bender, Lauretta, and Schilder, Paul: *Encephalopathia Alcoholicia (Polioencephalitis Haemorrhagica Superior of Wernicke)*. Arch. Neurol. & Psychiat. 29: 900-1053 (May) 1933.

14. Meyer, Jacob, and Scher, Eleanore: A Study of the Occupational Adjustment of Patients with Peptic Ulcer. Rev. Gastroenterol. 5: 54-64 (March) 1938.

15. Thompson, H. L.: Acute Perforation of Peptic Ulcer: Immediate and Late Results in Five Hundred Cases. J. A. M. A. 113: 2015-2018 (Dec. 2) 1939; personal communication to the author.

immediately after the patient sat up in bed. There was consistent hypothermia, with the temperature ranging from 97 F. to 97.8 F. The respiratory rate in bed ranged from 20 to 28. The blood pressure was 102 systolic and 64 diastolic. The dextrose tolerance test showed hypoglycemia, the sugar content being 45.1 mg. per hundred cubic centimeters at the end of the third hour. Gastric analysis revealed hypochlorhydria, the hydrochloric acid content of the gastric juice being 8 per cent. The basal metabolic rate was  $-2$  per cent. The blood count and urinalysis were essentially normal; the Wassermann test gave negative results.

A diagnosis of psychoneurosis and neurasthenia with autonomic imbalance was made. The present illness was regarded as being consequent to healed hemorrhages (Wernicke's encephalopathy) located chiefly in the parasympathetic areas of the hypothalamus and medulla, permitting alterations of metabolism and a too ready release of sympathetic manifestations.

*Treatment and Course.*—The patient was told that she was suffering from an organic disability and was asked to accept the handicaps which it entailed. This helped to resolve the depression and some of the anxiety which were based on the belief that she was lacking in character because she could not accomplish the usual amount of work. After a preliminary rest in bed of two weeks, a program calling for ten hours of rest in bed at night and two hours of rest in bed after lunch was advised. Minimal amounts of pentobarbital sodium ( $\frac{1}{2}$  grain, or 0.03 Gm.) were adequate for a full night's sleep. Diluted hydrochloric acid, 15 minims (0.92 cc.) with each meal, for the hypochlorhydria and vitamin B<sub>1</sub> (thiamine hydrochloride), 10 mg. daily, were ordered. A high caloric and high fat diet, with five meals a day, was utilized to correct the hypoglycemic trend.

With the measures instituted there was a gain in weight of 15 pounds (6.8 Kg.) in the following two months. Emotional disturbances subsided. Fatigue, breathlessness and palpitation continued to be in evidence after exertion but much less than formerly, and the patient was able to return to half-time work, at which she continues at the present time.

#### CONCLUSIONS

Acute Wernicke's encephalopathy may occur with many forms of severe disease of the abdominal viscera, and chronic residual damage to the autonomic and metabolic areas of the central nervous system may persist. Such damage may be reflected in certain conditions variously diagnosed as psychoneurosis, neurasthenia, autonomic imbalance or neurocirculatory asthenia. The treatment is based on the psychotherapeutic procedure of permitting the patient to recognize an organic handicap, on a program of regulated rest and activity and on symptomatic treatment of metabolic disturbances and avitaminosis.

#### ABSTRACT OF DISCUSSION

DR. ROBERT G. GREEN, Minneapolis: I should like to call attention to the widespread occurrence of a disease similar to Wernicke's among animals which is definitely associated with the feeding of fresh fish. For years I have been attempting to learn about virus diseases by systematically studying fur-bearing animal populations, and one of the most devastating outbreaks of disease that I have encountered has been a disease that we called Chastek paralysis, as it was first recognized on the fox ranch owned by Mr. Chastek. After years of investigation we came to realize that this was a vitamin B<sub>1</sub> deficiency disease, and it appears to be identical with Wernicke's disease. Fur animal populations differ from a human population in that all individuals receive exactly the same diet. Records are complete, so that one can study the feeding records before and after the appearance of the disease. All these outbreaks have been associated with the feeding of fresh fish and often as a part of a diet that would appear to be quite adequate in vitamins, and especially vitamin B<sub>1</sub>. I have also seen outbreaks occur where fox ranchers have fed their foxes rather large amounts of cod liver oil. We have consistently produced Chastek paralysis in

foxes simply by adding 30 per cent of fish to what had been a diet adequate in all respects before. This indicates that in some way the feeding of raw fish may be associated with the destruction of vitamin B<sub>1</sub>.

DR. NORMAN JOLLIFFE, New York: It is my belief that probably all the syndromes mentioned by Dr. Vonderahe represent one of the types of nutritional encephalopathy. The best defined of these has been labeled "nicotinic acid deficiency encephalopathy" (THE JOURNAL, Jan. 27, 1940, p. 307) and is characterized by clouding of consciousness, changing cogwheel rigidities of the extremities, and uncontrollable grasping and sucking reflexes. Another nutritional encephalopathy is one characterized by clouding of consciousness, cerebellar ataxia, ophthalmoplegia (complete or partial) and pupillary changes. I believe that the first syndrome represents an acute complete nicotinic acid deficiency, while the second represents an acute complete thiamine hydrochloride deficiency. More frequently than not one finds superimposed on these syndromes a delirious picture, a catatonic reaction, a cerebellar syndrome, or Korsakoff psychosis, in addition to polyneuropathy and the ordinary signs of pellagra. Under rare conditions each of these syndromes may occur alone, but usually two or more occur simultaneously, giving a confused clinical picture and a variety of pathologic findings. This confusion will persist as long as the combination of these syndromes is indiscriminately labeled under one diagnosis which varies with the hospitals and includes such terms as "wet brain," "central neuritis," "encephalopathy," "pseudo-Wernicke" and "Wernicke's disease." If ophthalmoplegia is present with one or more of the other syndromes I agree that the diagnosis of Wernicke's syndrome is justified. If ophthalmoplegia is not present I do not agree, however, with lumping together all the other nutritional encephalopathies under one label, such as "pseudo-Wernicke's." I believe that each patient should be labeled as to the clinical syndrome or syndromes presented, the response of each of the syndromes to specific crystalline vitamins recorded, and finally the pathologic changes found in each subject correlated with the clinical syndromes presented during life. If this is done it will eventually be possible to label each of these syndromes etiologically and anatomically and possibly administer the indicated specific nutritional substances necessary to initiate recovery.

DR. JOHN F. FULTON, New Haven, Conn.: I should like to ask Dr. Vonderahe what he considers the cause of the hemorrhagic lesions described. He has mentioned that, following acute abdominal episodes or associated with these episodes, hemorrhages are found. In long-standing cases evidence is present of old hemorrhage. Is it his opinion that the hemorrhage in the central nervous system precipitates the gastrointestinal crisis or that the gastrointestinal crisis through sensory innervation somehow irritates the centers in the hypothalamus and medulla and in that way secondarily causes the hemorrhage? I ask this because experimentally I have seen, following small lesions of the middle hypothalamic nuclei, acute petechial hemorrhages of the gastric mucosa, occasionally acute perforations and gastromalacia; and Dr. Zimmerman has reported a series of cases in which, following lesions of the central gray of the aqueduct, acute gastric hemorrhages occurred, or acute perforations. In the case of Dr. Zimmerman's evidence, the same question I suppose might be asked that I have asked Dr. Vonderahe: Which is cause and which is effect?

DR. A. R. VONDERAHE, Cincinnati: With respect to the role of vitamin B<sub>1</sub> deficiency, I think one application might be considered, namely the use of vitamin B<sub>1</sub> prior to operation as a prophylaxis against the production of such hemorrhages. I was interested in the comments of Dr. Jolliffe on terminology. It might be interesting to go back to the first description of these hemorrhagic findings by Wernicke himself, who was anxious, it seems, to build up a clinical entity comparable to the brain stem to that of anterior poliomyelitis in the spinal cord. For this reason he coined the term acute hemorrhagic polioencephalitis superior. But anterior poliomyelitis, as the years went on, was found to be a definite infectious disease, while so-called Wernicke's disease remains a pathologic complex producible by many different agents. Wernicke's first patient was not alcoholic; the other two that he described were alco-



holic. As time went on, the role of alcoholism was accentuated, so that one finds in some textbooks that the term "Wernicke's disease" is limited to alcoholism. Because of these factors, confusion has crept in. Wernicke's disease is not a characteristic disease entity. It occurs in alcoholism and it occurs, as we have seen here today, in a wide variety of other conditions. I am grateful to Dr. Fulton for asking this question. I believe that the recent hemorrhages in cases of gastric ulcer are effects. However, in patients who recover, the healed hemorrhages act as foci for a new cycle of autonomic disturbance. The cause of gastric ulcer is still undetermined. I think what I have to say can best be illustrated with a case which presented a history of gastric ulcer and at autopsy presented a gastric carcinoma. There were also small, bilateral, symmetrically placed meningiomas pressing on area 6, which, I would be inclined to think, may have caused the ulcer, while the changes occurring in the hypothalamus were secondary, perhaps associated with vitamin B<sub>1</sub> deficiency. I think that in the case of man we have to bear in mind the continuation of life once a disease is started. Man is not sacrificed when he develops an ulcer. His ulcer goes on, and its effects are reflected elsewhere in the altered condition of his body. These in turn produce other effects, and the cycle, which includes the changes in the central nervous system, continues onward until death.

## THE USE OF DESICCATED PLASMA

WITH PARTICULAR REFERENCE TO SHOCK

J. M. HILL, M.D.

E. E. MUIRHEAD, M.D.

C. T. ASHWORTH, M.D.

AND

W. D. TIGERTT, M.D.

DALLAS, TEXAS

Of the many problems in the field of surgery today, none are of more vital interest than the closely correlated problems of shock, fluid balance, blood volume and plasma proteins. The importance of this aspect of surgery has been emphasized by the present war and an urgent impetus imparted to its study.

In the belief that plasma proteins are the key to these surgical problems, this report of the results obtained by the operation of a routine desiccated plasma service is given. This service, operated in conjunction with the Baylor University blood bank during the last sixteen months, has made plasma of any desired concentration or amount available day or night in a manner comparable to ordinary intravenous fluids.

Our purpose in this paper in describing this service and its results is to point out the advantages and practicability of supplying concentrated plasma, prepared by redissolving the dry lyophilic form obtained through desiccation from the frozen state. We believe that plasma prepared in this manner exhibits in a greater degree not only all the desirable properties claimed for whole plasma but also unique additional advantages both technical and therapeutic, which are inherent in the desiccation and the concentration thereby made possible. The technical advantages of desiccation and concentration relating to storage, transportation, simplicity and speed of administration have been discussed in an earlier paper<sup>1</sup> on the new

inexpensive desiccation method, the adtevac process. The importance of these practical technical factors should not be minimized, particularly in connection with military requirements.

However, the therapeutic advantages are even more significant and can be attributed chiefly to the control of osmotic forces made possible by choice of concentration up to four or five times normal. These advantages of concentrated plasma suggest three principal groups of indications: first, the regulation of blood volume; second, control of plasma protein levels, and third, special adjustment of fluid balance when marked hypertonic effects are essential.

Restoration of circulating blood volume is the essential aim of the treatment of shock, regardless of its cause, whether hematogenic, neurogenic, vasogenic or strictly posthemorrhagic. The part played by these causative factors is highly controversial and need not be considered here. However, there is general agreement with regard to the general mechanism of shock, namely a disparity in blood volume relative to vascular capacity. Blalock<sup>2</sup> and Moon<sup>3</sup> particularly have emphasized this point and stressed the importance of plasma loss from damaged capillaries. A vicious cycle tends to be set up, with progressive vascular damage resulting from anoxemia. The more profound the shock, the more urgent is the necessity for a speedy reversal of this mechanism before irreparable damage occurs.

As was previously indicated,<sup>4</sup> concentrated plasma appears ideal for this purpose for several reasons. First, larger amounts of protein can be more speedily placed in the circulation than by any other method, a point of importance in view of Minot and Blalock's<sup>5</sup> suggestion of the value of giving colloid fast enough to increase its level to the point of retaining effective circulating volume in spite of concomitant losses. Furthermore, hypertonic plasma tends to effect an immediate reversal of the abnormal physiologic changes of shock. Blood volume is built up by immediate withdrawal from the tissues of fluid previously lost from the blood stream. Finally it seems probable that concentrated plasma has a direct stimulating effect on vascular tone and permeability. King<sup>6</sup> showed increased effectiveness of hypertonic fluids in his work demonstrating the superiority of hypertonic over physiologic solution of sodium chloride, indicating direct vascular stimulation in shock cases. The work of Krogh and Harrop<sup>7</sup> and of Drinker<sup>8</sup> demonstrated the importance of plasma proteins or associated substances in the maintenance of capillary tone and normal permeability. The evidence suggested that the concentration of these substances was a favorable factor.

The second group of indications for plasma therapy is concerned with the control of plasma protein levels, a problem of increasing importance in modern surgery.

2. Blalock, A.: *Principles of Surgical Care: Shock and Other Problems*, St. Louis, C. V. Mosby Company, 1940.

3. Moon, V. H.: *Shock and Related Capillary Phenomena*, New York, Oxford University Press, 1938.

4. Hill, J. M.: *Intravenous Use of Concentrated Plasma Prepared by the Adtevac Process*, Texas State J. Med. **36**: 223, 1940. Hill and Pfeiffer.<sup>1</sup>

5. Minot, A. S., and Blalock, A.: *Plasma Loss in Severe Dehydration: Shock and Other Conditions as Affected by Therapy*, Ann. Surg. **112**: 557, 1940.

6. King, R. A.: *Methods of Fluid Administration in the Treatment of Surgical Shock: An Experimental Comparison*, Brit. M. J. **2**: 485, 1940.

7. Krogh, A., and Harrop, G. A.: *On the Substance Responsible for Capillary Tonus*, J. Physiol. **54**: 125, 1921.

8. Drinker, C. K.: *The Permeability and Diameter of the Capillaries in the Web of the Brown Frog (R. Temporaria) When Perfused with Solutions Containing Pituitary Extract and Horse Serum*, J. Physiol. **63**: 249, 1927.

Aided by a grant from the Abbott Laboratories.

From the Department of Pathology, Hospital Laboratory Division, Baylor University College of Medicine.

1. Hill, J. M., and Pfeiffer, D. C.: *A New and Economical Desiccating Process Particularly Suitable for the Preparation of Concentrated Plasma or Serum for Intravenous Use: The Adtevac Process*, Ann. Int. Med. **14**: 201 (Aug.) 1940.

The quantities of protein required to combat hypoproteinemia make it highly desirable to give this type of intravenous feeding in concentrated form. By this means blood protein levels can be rapidly raised and sustained when suitable amounts are given. Furthermore, the work of Madden and Whipple<sup>9</sup> indicates not only that plasma is an ideal food for all cellular protein requirements but also that saturation of plasma protein storage depots is important in the production of antibodies.

In this connection we would also point out that prolonged preservation of antibodies, prothrombin and complement in plasma can be accomplished only by desiccation from the frozen state. The application of these facts to the treatment of infections by concentrated plasma is obvious.

The third group of indications for concentrated plasma involves special hypertonic effects required to accomplish substantial shifts of fluid. Reduction of increased intracranial pressure by concentrated plasma as reported by Hughes, Mudd and Strecker<sup>10</sup> is an example of such uses. For these purposes hypertonic plasma proteins are superior because of the prolonged osmotic effect. Surgical complications resulting from edema associated with hypoproteinemia logically fall in this group and show a rapid response to intravenous concentrated plasma. Ravdin<sup>11</sup> has reviewed this problem.

Experimental evidence of the value of concentrated serum in shock was first demonstrated by Bond and

Magladery, Solandt and Best,<sup>14</sup> in a later report, denied any advantage of concentrated serum over an equal volume of whole serum in the treatment of post-hemorrhagic shock.

Clinical interest in the plasma proteins has been reflected chiefly in the expanding literature on the use of whole plasma. In the treatment of shock, reference should be made to the work of Levinson, Rubovits and

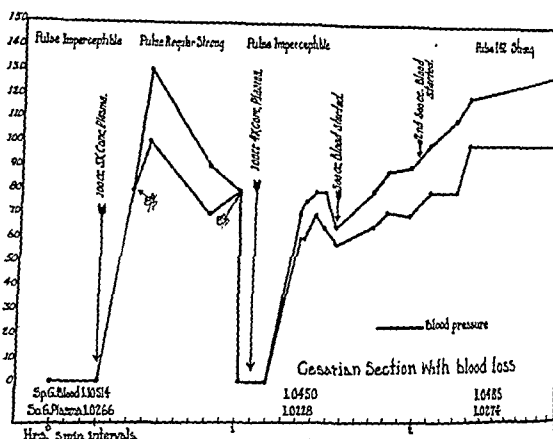


Chart 2.—Blood pressure in case 3.

Neches,<sup>15</sup> of Strumia, Wagner and Monaghan<sup>16</sup> and of Brennan,<sup>17</sup> while in burns the reports of Elkington, Wolff and Lee,<sup>18</sup> of McClure<sup>19</sup> and of Minot and Blalock<sup>5</sup> are outstanding. This use of whole plasma represents a definite advance in the therapy of shock and burns. Nevertheless, we believe, full realization of all the potentialities of plasma proteins is possible only if choice of concentration is made available by desiccation.

The numerous reports on the use of whole plasma is in marked contrast to the restricted clinical use of concentrated plasma and serum. Hughes, Mudd and Strecker<sup>10</sup> in 1938 described the successful treatment of seven cases of increased intracranial pressure. No clinical reports in the field of surgery have since been observed which included any series of cases treated by concentrated plasma, although a preliminary summary of clinical results was given by Hill<sup>4</sup> and by Hill and Pfeiffer.<sup>1</sup> The treatment of nephrosis with concentrated serum, as emphasized by Aldrich and his associates,<sup>20</sup> represents an example of this type of therapy in the medical field. Hypertonic plasma has been used, however, in a variety of isolated cases included in the many papers on whole plasma.

#### METHODS

Since in the past the chief obstacle to the use of concentrated plasma has been the technical difficulty

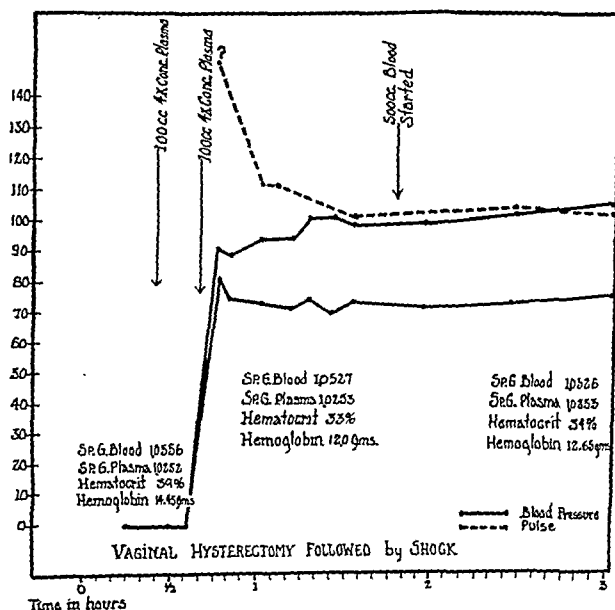


Chart 1.—Blood pressure and pulse in case 1. Blood pressure points have been plotted as 0 when the pressure was unobtainable by the ordinary methods.

Wright.<sup>12</sup> More recently Best and Solandt<sup>13</sup> found that concentrated serum was effective in the treatment of traumatic shock and hemorrhage in dogs. However,

9. Madden, S. C., and Whipple, G. H.: Plasma Proteins: Their Source, Production and Utilization, *Physiol. Rev.* 20:194, 1940.

10. Hughes, Joseph; Mudd, Stuart, and Strecker, E. A.: Reduction of Increased Intracranial Pressure by Concentrated Solutions of Human Lymphoid Serum, *Arch. Neurol. & Psychiat.* 39:1277 (June) 1938.

11. Ravdin, I. S.: Hypoproteinemia and Its Relation to Surgical Problems, *Ann. Surg.* 112:576, 1940.

12. Bond, D. D., and Wright, D. G.: Treatment of Hemorrhage and Traumatic Shock by the Intravenous Use of Lymphoid Serum, *Ann. Surg.* 107:500, 1938.

13. Best, C. H., and Solandt, D. Y.: Use of Plasma or Serum as a Substitute for Whole Blood, *Brit. M. J.* 1:116, 1940.

14. Magladery, J. W.; Solandt, D. Y., and Best, C. H.: Serum and Plasma in Treatment of Hemorrhage in Experimental Animals, *Brit. M. J.* 2:249, 1940.

15. Levinson, S. O.; Rubovits, F. E., and Neches, Heinrich: Human Serum Transfusions, *J. A. M. A.* 115:1163 (Oct. 5) 1940.

16. Strumia, M. M.; Wagner, J. A., and Monaghan, J. F.: Treatment of Secondary Shock, *J. A. M. A.* 114:1337 (April 6) 1940.

17. Brennan, H. J.: Plasma Transfusions in the Treatment of Hemorrhage, *Brit. M. J.* 1:1047, 1940.

18. Elkington, J. R.; Wolff, W. A., and Lee, W. E.: Plasma Transfusion in the Treatment of the Fluid Shift in Severe Burns, *Ann. Surg.* 112:150, 1940.

19. McClure, R. D.: The Treatment of a Patient with Severe Burns, *J. A. M. A.* 113:1809 (Nov. 11) 1939.

20. Aldrich, C. A.; Stokes, Joseph, Jr.; Killingsworth, W. P., and McGuiness, A. C.: Human Blood Serum as a Diagnostic Agent in Treatment of Nephrosis, *J. A. M. A.* 111:129 (July 9) 1938.

Boyle, H. H.: Concentrated Human Blood in the Treatment of Nephrosis; Further Observations, *J. A. M. A.* 114:1062 (March 25) 1940.

of desiccation from the frozen state, it seems advisable to outline briefly the methods employed in our plasma service.

Plasma is obtained in part as a by-product of the blood bank and in part from blood taken directly for this purpose. A completely neutral plasma is produced by adsorption of agglutinins when the different types of whole blood are pooled at low temperature as described in an earlier paper.<sup>21</sup> It was found practicable to neutralize as much as ten parts of type O plasma with one part of type AB or one part each of types A and B whole blood. Edwards, Kay and Davie<sup>22</sup> have employed the same principle, but using only equal parts of A and B blood. When serum is used, the same technic is applied by defibrinating blood as it is drawn making cells and serum available.

The neutral plasma or serum is placed in large ampules of 500 cc. capacity and desiccated in bulk from the frozen state by the inexpensive adtevac process, by which moisture contents below 1 per cent are easily attained. At first the dry material was made into a four times concentrate and stored frozen in a low temperature refrigerator. Recently the dry material has been granulated in a special dispensing device, weighed and placed in vaccine type bottles. Either a vacuum is drawn or dry nitrogen introduced by way of a hypodermic needle, and the rubber cap sealed with celloidin. A dose of 25 Gm. is accompanied by sufficient water to make up 100 cc. of concentrate. All water used is strictly pyrogen free to avoid reactions.<sup>23</sup>

Practically all the plasma was given as the four times concentrate, a syringe of 50 or 100 cc. size and a 19 or 20 gage needle being used. On occasions when transfusions were already started the plasma was injected into the rubber tubing, which was temporarily clamped off above. In shock the dose was given rapidly, up to 100 cc. per minute. In other conditions the speed was judged by the apparent integrity of the cardiovascular system. Frequently an injection period of five

22,220 cc. of four times concentrated plasma has been given to 156 hospital patients, while 8,295 cc. has been given to an undetermined number of outside patients, a total of 30,515 cc., requiring over one-fourth million cc. of blood for its preparation.

After removing the 45 closely followed cases of shock for separate analysis there remains a heterogeneous group of 111 cases summarized in table 1. It

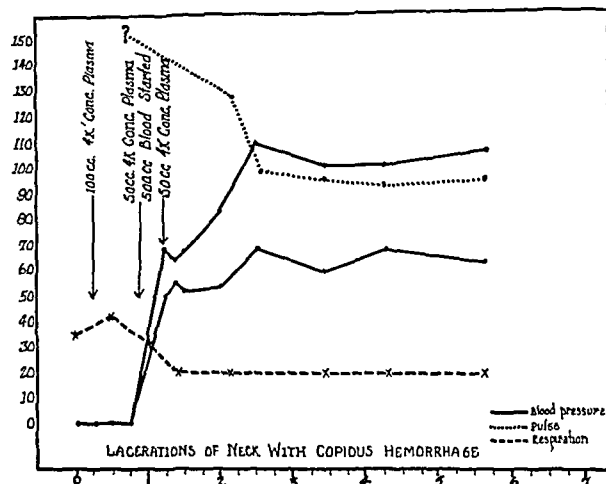


Chart 3.—Blood pressure, pulse and respiration in case 16.

is not within the scope of this paper to report in detail the results of treatment in all the diverse conditions represented. However, it can be stated that no harmful effects were noted, some benefit was obtained in practically every case and impressive results were observed in several. The obstetric group including the successful treatment of eclampsia with hypertonic plasma will be reported elsewhere.

Special mention should be made concerning the effects of concentrated plasma in surgical conditions other than shock. In complications associated with hypoproteinemia, such as saline edema, closure of anastomosis stomas, pulmonary edema and pneumonia, and retarded wound healing, concentrated plasma yielded excellent results in prevention and treatment.

The 45 cases of shock are summarized in table 2. Of this number 19 were considered as severe, 16 moderate and 10 mild. This classification, of course, is an arbitrary one based on criteria not as clear cut as could be desired. Severe cases were those with imperceptible pulse or blood pressure, or with profound mental depression on down to coma. Moderate cases were those presenting blood pressures definitely below the so-called critical level usually assumed to be 80 systolic and 40 diastolic. In mild cases the blood pressure was in the vicinity of this level with other signs of shock being exhibited. All cases showed the common signs of peripheral circulatory failure, namely sweating, pallor, cold clammy skin, mild cyanosis and rapid pulse.

The results of treatment were graded as excellent when the blood pressure was elevated above the critical level or higher in from five to thirty minutes, as fair when improvement was slower or less pronounced, and as poor when the response was transitory or absent. On this basis the results were excellent in 36 cases, fair in 8 and poor in 1. In this group of 45 cases some degree of hemorrhage was a factor contributing to shock in 36 instances. Some type of surgical procedure was performed in 37 cases, each not necessarily

TABLE 1.—Summary of 111 Cases

	No. of Cases	No. of Doses	Total No. of Cc.	Average Dose
.....	10	18	850	47 cc.
.....	23	49	4,605	94 cc.
.....	19	49	2,820	58 cc.
Severe infections and terminal collapse.....	16	26	1,925	74 cc.
Neurosurgery and head injuries.....	21	32	2,975	74 cc.
Burns.....	6	15	1,230	89 cc.
.....	3	7	355	50 cc.
.....	2	6	260	43 cc.
.....	11	10	845	85 cc.
Total.....	111	299	15,355	68.2 cc.

minutes was satisfactory for the average 100 cc. dose. In cases in which a sudden increase of blood volume was considered dangerous, slower rates up to twenty minutes were recommended. Blood pressures were frequently checked during administration when very large amounts were given.

When possible, relative blood volume changes were followed by laboratory tests, such as blood and plasma specific gravity determinations, hematocrit, red cell count and photoelectric hemoglobin estimations.

#### CLINICAL DATA

The plasma service has been in operation approximately one and one-half years. During this period

21. Hill.

22. Edwards, F. R.; Kay, J., and Davie, T. B.: The Preparation and Use of Dried Plasma for Transfusion, *Brit. M. J.*, 1: 377, 1940.

23. Seibert, F. B.: Fever Producing Substances Found in Some Distilled Waters, *Am. J. Physiol.*, 67: 90, 1923.

TABLE 2.—Observations in 45 Cases of Shock

Case	Age	Type of Case	Degree of Shock	Blood Pressure	Radial Pulse	Specific Gravity Blood	Specific Gravity Plasma	Hemato- crit Hemo- globin	Amount 4x Concentrated Plasma	Other Measures	Comment
1	46	Vaginal hysterectomy	Severe	Imperceptible 92/84 104/78	Imperceptible Just palpable 112	1.0556 1.0527	1.0252 1.0253	49% 14.5G 33% 12.00G	200 cc.	500 cc. blood after shock controlled	100 cc., slight improvement; second 100 cc. and B. P. to 92/84 in 10 min., less restless; blood given and B. P. to 110/80, p. 108
2	34	Two incidents: (1) Hemorrhage from duodenal ulcer  (2) Operation for the ulcer and hemorrhage	Moderate  Severe	63/55 108/75  Imperceptible 88/44 Imperceptible 120/80	92 weak 88  Imperceptible Weak Imperceptible 140	1.0536 1.0532 1.0519 1.0500	1.0220 1.0235 1.0243 1.0234	37% 34.5% 37% 36%	150 cc.  230 cc. 380 cc.	.....  1,000 cc. whole blood being given when shock occurred	100 cc., B. P. to 80/55 in 10 mins.; then 50 cc. and B. P. to 108/75 in 20 mins.; R. B. C. remained in vicinity of 3,500,000  350 cc. blood given when shock occurred; 100 cc. elevated B. P. to 88/44 in 5 mins.; 15 mins. later B. P. imperceptible; 65 cc. and repeated and B. P. to 80/? in 8 mins.; 90/70 in 20 mins.; later 120/80, P. 140, R. B. C. from 3,340,000 to 3,140,000
3	32	Cesarean section; glomerulonephritis	Severe	Imperceptible 130/100 Imperceptible 110/80	Imperceptible Palpable Imperceptible 140	1.0514  1.0450 1.0485	1.0265  1.0228 1.0274	31%  25% 25%	350 cc.	1,000 cc. blood	150 cc. 2 days before operation; shock at operation, 100 cc. gave temporary results; a second 100 cc. and B. P. from imperceptible to 80/70 in 10 mins.; 1,000 cc., blood and B. P. to 110/80
4	66	Copious hemorrhage during removal of large adenocarcinoma of kidney	Severe	Imperceptible 85/50 110/76	Imperceptible 134 strong 100	1.0516 1.0497 1.0352	1.0241 1.0259 1.0210	28% 24%	150 cc.	500 cc. blood and 500 cc. saline after shock controlled	100 cc. and B. P. to 85/50 in 10 mins.; 1½ hrs. later B. P. 49/?; then 40 cc. and B. P. to 74/50 in 20 mins.; later B. P. 110/50; R. B. C. in vicinity of 2,600,000
5	29	Hemorrhage, post partum, profuse	Severe	63/40 94/70 120/80	104 weak Stronger Strong	1.0520  1.0478	1.0282  1.0238	34%  27%	165 cc.	500 cc. blood and 1,000 cc. 5% dextrose in saline after shock controlled	Semicomatose, B. P. 65/40; 100 cc. and in 5 mins. B. P. 75/60; in 20 mins. B. P. 94/70; later 120/80
6	45	Breast operation and hemorrhage	Severe	..... 130/80 110/72	Imperceptible Strong 88	1.0463 1.0434 1.0380	..... 1.0231 Very low	..... 30% 28%	155 cc.	700 cc. 5% dextrose in saline just before and shortly after concentrated plasma	No pulse, cold, pale, sweating. B. P. not taken; 100 cc. and in 10 mins. B. P. 130/80; later 55 cc. and B. P. 110/72
7	20	Prolonged labor, no excessive bleeding	Severe	70/?* 100/74 124/84	Imperceptible 140 132	1.0428 1.0438 1.0340	..... 1.0246 1.0276 1.0275	..... ..... .....	200 cc.	.....	90 cc. and B. P. to 80/? in 10 mins.; 110 cc. and B. P. to 96/76 in 5 mins.; later B. P. 124/84
8	25	Perforated appendix; spinal anesthesia	Severe	40/? 90/55 106/65	Imperceptible 120 140	1.0488 1.0484 1.0496	1.0246 1.0276 1.0275	..... ..... .....	110 cc.	Ephedrine with no results	After 110 cc., B. P. to 80/60 in 5 mins., to 90/55 in 9 mins.
9	27	Bullet wounds through chest	Severe	65/30 94/60 114/84	140 140 130	1.0632 1.0608 1.0581	1.0276 1.0281 1.0285	..... ..... .....	180 4x 100 5x 280 cc.	500 cc. 5% dextrose in saline with no response	80 cc. and B. P. to 75/50 in 20 mins.; 100 cc. and B. P. to 94/60 in 35 mins.; 8 hrs. later B. P. 96/80 and 100 cc. 5x conc. given; B. P. to 114/84 in 3 hrs.
10	5 mos.	Spina bifida, myelomeningocele, operation	Severe	.....	Imperceptible Palpable regular	.....	.....	.....	18 cc.	40 cc. saline by hypodermoclysis after shock controlled	Pulse imperceptible; sweating, cyanotic, condition considered critical; 18 cc. and in 5 mins. pink, ceased sweating; in 10 mins. pulse palpable
11	48	Pelvic operation, bulky fibroid, myoma of uterus	Severe	75/60 110/80 60/? 110/80	110 weak 120 120 110	.....	.....	.....	100 cc.	1,000 cc. 5% dextrose in saline followed by shock; 500 cc. blood	50 cc., B. P. to 110/80 in 10 mins.; additional 50 cc.; 50 mins. later B. P. 60/?; blood helped elevate it to 110/80
12	42	Vaginal hysterectomy followed by shock	Severe	Imperceptible 70/? Imperceptible	Imperceptible Just palpable Imperceptible	.....	.....	.....	170 cc.	1,000 cc. blood and 1,000 cc. saline	Shock 1½ hrs. after operation with gradual onset; slight temporary improvement with each dose; patient died
13	45	Carcinoma of cervix with hemorrhages	Severe	50/30 105/80 100/70	Imperceptible 80 90	.....	.....	.....	100 cc.	1,000 cc. 5% dextrose in saline	Clinical improvement before much saline taken; B. P. to 105/80 in 30 mins.; later 50 cc. maintained B. P. at 100/70
14	40	Lung abscess with lobectomy	Severe	Imperceptible Not taken 76/60 100/60	Imperceptible 130 104 110	.....	.....	.....	100 cc.	500 cc. blood and 500 cc. saline	During operation 2,000 cc. saline and 500 cc. blood given; 20 mins. later sweating, pale, cool, unable to get B. P. or pulse; 100 cc. with blood, B. P. 75/50, 3½ hrs. later; later 100/60
15	23	Ruptured tubal pregnancy	Severe	Imperceptible 72/44 Normal	Imperceptible Weak 84 strong	.....	.....	.....	75 cc.	500 cc. blood and 500 cc. saline	Deep shock, 75 cc. and B. P. from imperceptible to 65/? in 5 mins., to 68/40 in 20 mins., to 72/44 in 40 mins.; then blood given and B. P. normal, pulse 81

\* Question mark signifies that only few impulses heard and no definite diastolic level discernible.

TABLE 2.—Observations in 45 cases of Shock—Continued

Case	Age	Type of Case	Degree of Shock	Blood Pressure	Radial Pulse	Specific Gravity Blood	Specific Gravity Plasma	Hemato- crit Hemoglobin	Amount 4× Concentrated Plasma	Other Measures	Comment
16	55	Lacerations of neck with copious hemorrhage	Severe	Imperceptible - 70/50 100/58	Imperceptible 94	.....	.....	....	300 cc.	500 cc. blood and 500 cc. saline	Comatose, cyanotic, sweating, cold, B. P. and pulse imperceptible, respirations sporadic; 100 cc. and began to move, sweating ceased; 100 cc. more, 500 cc. blood started and in 25 mins. B. P. 70/50; in 1 hr. B. P. to 100/58; next day 50 cc. and B. P. stabilized
17	19	Fracture of right femur and laceration	Severe	75/? 118/65	160 weak 140 strong	.....	.....	....	200 cc.	500 cc. blood and 500 cc. saline	On admission B. P. 125/70, pulse 88; patient restless and 100 cc. given; while 500 cc. blood given, patient into shock; 100 cc. and B. P. to 90/20 in 10 mins., to 88/50 in 25 mins., to 118/65 in 1 hr.
18	21	Head injury, subarachnoid hemorrhage, compound fracture	Severe	40/? 60/30 110/70 Imperceptible	Imperceptible Just palpable Strong Imperceptible	.....	.....	....	255 cc.	.....	Severe shock, 100 and 75 cc. doses, in 20 mins. B. P. 60/30, in 30 mins, 110/70; 1 hr. later B. P. and pulse imperceptible, and 2 hrs. later patient died
19	53	Malaria, history of blood in stool and vomitus	Moderate	60/? 70/50 92/70	100 96 83	1.0579 1.0519	1.0214 1.0210	46% 15.55G 40% 13.25G	150 cc.	500 cc. blood	500 cc. blood and 30 cc. and B. P. to 64/50 in 25 mins.; 5 mins. after 70 cc., B. P. 70/50; 50 cc. more and B. P. 92/70; later 120/70
20	18	Operation, spinal fusion	Moderate	55/20 70/54 80/60	Imperceptible 120 116	1.0527 1.0510 1.0491	..... ..... .....	41% 13.55G 11.75G 12.35G	100 cc.	.....	50 cc. in O. R., gradual response; 50 cc., B. P. to 70/54 in 45 mins.; third 50 cc. and B. P. 76/60; 90 cc., B. P. to 80/60, later 110/80
21	41	Radical mastectomy	Moderate	64/ no change 80/30 64/30 94/64	150 weak 140 stronger 140 144	1.0478 ..... 1.0427	1.0295 ..... .....	30% 7.9G ..... 24%	150 cc.	.....	100 cc. and B. P. to 80/30 in 9 mins., then down to 64/30 7 min. later; 50 cc. and B. P. to 80/55 in 20 mins.; later 94/64 and 110/70
22	18	Cervical dissection for malignant melanoma	Moderate	65/? 85/45 110/70	Weak and fast Stronger 126	1.0613 1.0597 1.0532	1.0299 1.0298 1.0254	38% 35% 32%	100 cc.	1,000 cc. 5% dextrose in saline followed by shock	100 cc. and B. P. to 85/45 in 15 mins.; in 20 mins. 95/60, to 110/70 35 mins. after given
23	91	Hemorrhage, about 1,000 to 1,500 cc. lost	Moderate	80/70 130/74	Weak Strong	1.0504 1.0539	1.0273 1.0262	30% 36%	100 cc.	500 cc. blood and 500 cc. saline after shock controlled	50 cc. and B. P. to 100/70 in 20 mins.; 50 cc. more and B. P. to 130/74
24	32	Multiple fractures of pelvis and right leg	Moderate	50/40 80/50 100/60	93 80 60	1.0547 1.0530 1.0528	1.0260 1.0258 1.0253	40% 31% 31%	55 cc.	1,000 cc. 5% dextrose in saline started at same time plasma given	In 10 mins. B. P. to 65/45; in 2½ hrs. 86/54, later 120/70; R. B. C. 4,000,000 to 3,300,000
25	23	Multiple fractures and lacerations	Moderate	78/45 115/72	Weak 90 strong	1.0635 1.0529	1.0270 1.0291	.....	150 cc.	500 cc. blood after shock controlled	50 cc. given because of mounting blood sp. gr.; 1 hr. later B. P. 78/48; 100 cc. and B. P. 115/92 in 15 mins.
26	16	Operation, open reduction	Moderate	84/? 94/52 100/70	Imperceptible Imperceptible 150	1.0659 1.0609 1.0570	1.0311 1.0314 1.0303	.....	100 cc.	.....	Shock; B. P. 84/? but in 2 hrs. B. P. 94/52; 100 cc. and B. P. to 100/70 in 20 mins.
27	40	Pelvic operation, hysterectomy and salpingectomy	Moderate	60/? 94/70 103/80	Imperceptible 123 120	1.0589 ..... 1.0583	1.0312 ..... 1.0303	.....	100 cc.	500 cc. blood and 500 cc. saline	Shock after all of blood taken; 50 cc. and B. P. to 90/? in 20 mins.; then 50 cc. and B. P. to 94/70 15 mins. later; in 2½ hrs. B. P. 103/80
28	15	After normal delivery with about 700 cc. blood loss	Moderate	80/50 110/60 115/70	Weak 145 ...	1.0490 1.0480 1.0426	1.0274 1.0276 1.0251	.....	200 cc.	500 cc. blood and 500 cc. saline	Semicomatose, cold, sweating; 100 cc. and B. P. from 80/50 to 110/60 in 10 mins.; later 100 cc. and B. P. from 125/80 to 120/80 7 mins. later
29	54	Abdominoperitoneal resection of rectum	Moderate	60/? 75/40 100/64 100/60	Imperceptible 160 155 124	1.0522 ..... 1.0485 1.0440	..... ..... .....	.....	230 cc.	1,000 cc. 5% dextrose in saline followed by shock; later 1,000 cc. blood and 1,000 cc. saline	50 cc. elevated B. P. from 60/? to 75/40 in 10 mins.; 50 cc. more and B. P. 100/64 in 1½ hrs.; then 1,000 cc. saline and 50 cc. 4× conc. plasma; later blood and 100 cc. more given; R. B. C. from 4,150,000 to 2,620,000
30	15	Removal of large thoracic neuroblastoma	(1) Moderate (2) Moderate	80/60 105/80 85/60 105/60 100/70	Weak Strong ..... Questionable Stronger 162	..... ..... ..... .....	..... ..... .....	.....	100 cc. ..... 100 cc. 200 cc.	500 cc. blood and 500 cc. saline ..... 500 cc. blood and 500 cc. saline	Shock immediately after operation; 100 cc. elevated B. P. to 165/80 in 25 mins.; 500 cc. blood and B. P. 100/70 for 2 days Two days later shock, 100 cc. and B. P. to 103/60 in 20 mins.; B. P. remained 90/60 to 100/70

TABLE 2.—Observations in 45 Cases of Shock—Concluded

Case	Age	Type of Case	Degree of Shock	Blood Pressure	Radial Pulse	Specific Gravity Blood	Specific Gravity Plasma	Hemato- crit Hemo- globin	Amount 4× Concentrated Plasma	Other Measures	Comment
31	39	Pelvic operation, endometriosis	Moderate	74/60 96/60 112/78	Imper- ceptible 140 120	1.0520 1.0494 1.0494	1.0246	....	70 cc.	500 cc. blood after shock controlled	70 cc., B. P. to 96/60 in 10 mins.; later 112/78; R. B. C. 3,990,000 to 3,500,000
32	52	Hemorrhage, copious after prostatic reaction	Moderate	80/40 130/75	Weak Strong	.....	.....	....	100 cc.	2,000 cc. blood, 600 cc. saline and shock persisted	After 2,000 cc. blood patient remained pale, cold, sweating, very weak pulse; 100 cc. improved condition promptly
33	57	Hysterectomy and appendectomy	Moderate	80/50 134/84	Fast, weak 84	.....	.....	....	100 cc.	500 cc. blood and 500 cc. saline	1,000 cc. 5% dextrose in saline followed by shock; blood elevated B. P. to 110/60; 50 cc. and B. P. to 134/84; 50 cc. more and B. P. to 174/95
34	34	Bilateral salpingo-oophorectomy	Moderate	70/35 106/55	Very weak 130 strong	.....	.....	....	100 cc.	2,000 cc. 5% dextrose in saline followed by shock	100 cc. and B. P. to 106/55 in 15 mins.
35	26	Pelvic operation, large fibro-leiomyoma	Mild	74/55 80/60 90/60 90/60	130 124 112 104	..... 1.0503 1.0491 1.0593	..... 1.0251 1.0243 1.0234	.... 36% 35%	100 cc.	500 cc. blood after shock controlled	Mild shock, after operation, controlled although highest B. P. 90/60, P. 112; then blood given; R. B. C. 4,000,000 to 4,110,000
36	25	Multiple rib resection with blood loss	Mild	80/50 104/60	125 96	1.0578 1.0534	1.0338 1.0264	40% 40%	100 cc.	500 cc. blood	During operation pulse weakened and B. P. dropped; this was checked with 50 cc. plasma and 500 cc. blood; later B. P. 80/50 and 94/40; 50 cc. caused prompt rise to 104/60, where it remained
37	58	Partial gastrectomy	Mild	90/60 116/80	160 120	1.0542 1.0517	.....	.... 38%	175 cc.	1,000 cc. 5% dextrose in saline	60 cc. before operation, 55 cc. to control shock; 60 cc. terminally, R. B. C. 4,000,000 to 3,600,000
38	46	Partial gastrectomy	Mild	88/64 120/80	130 90	1.0525	1.0241	39%	110 cc.	500 cc. blood and 200 cc. saline	Moderate lowering of B. P. and weakening of pulse during operation and 60 cc. given; later B. P. 88/64; 50 cc. and blood elevated it to 120/80
39	45	Chronic blood loss and severe anemia, multiple fibro-leiomyomas	Mild	90/42 90/42	120 120	.....	.....	....	60 cc.	.....	Bleeding freely, very weak, pale, restless; known pyrogen containing water inadvertently used; patient had reaction
40	18	Left thigh amputation for osteogenic sarcoma	Mild	..... 112/70	156 weak 148 strong	.....	.....	....	100 cc.	1,000 cc. 5% dextrose followed by shock	Patient cold, pale, profuse perspiration, weak pulse; noticeable improvement after 60 cc. and B. P. 112/70, 10 mins. later
41	11	Gunshot wound of foot	Mild	.....	Weak, fast	.....	.....	....	75 cc.	1,000 cc. 5% dextrose in saline	Described as being in shock with improvement after 75 cc.
42	68	Colostomy	Mild	88/72 104/74 85/60	160 160 130	.....	.....	....	100 cc.	.....	Fast weak pulse, profuse sweating, declining B. P.; 100 cc. and B. P. 104/74 in 5 mins.; back to 98/74 5 mins. later, and sustained in that range
43	26	Abdominal pregnancy with severe hemorrhage	Severe	Imper- ceptible 65/50  100/60 Imper- ceptible 70/35 150/80	Imper- ceptible Just palpable 94 Imper- ceptible 100 112	..... ..... ..... ..... .....	..... ..... ..... ..... .....	39% 9.8G  23% 8.85G  7.2G 11.1G	400 cc.	4,000 cc. whole blood and 1,500 cc. saline, 50 cc. 50% dextrose solution	Estimated blood loss was 2,200 to 3,000 cc.; primary rise to 65/50 in 5 mins. with 130 cc.; in next 45 mins. 60 cc. plus 50 cc. 50% dextrose given and B. P. to 100/60; B. P. drop probably due to hemoglobin at critical level; 210 cc. elevated B. P. to 70/35; then 4,000 cc. blood and B. P. steadily to 120/80 and sustained
44	19	Traumatic injuries of face	Mild	90/40 110/70	64 weak 68 strong	.....	.....	....	50 cc.	.....	Patient cold, pale, sweating and mentally dull; 50 cc. and B. P. immediately to 110/70, sweating ceased, patient began talking rationally
45	25	Ruptured tubal pregnancy	Mild	74/60 126/70	96 weak Strong	.....	.....	....	100 cc.	.....	Cold, pale, respiration shallow, pulse weak, slightly cyanotic; 100 cc., B. P. to 126/70 in 25 mins., markedly improved

corresponding to cases in the former group. It should be understood that analysis of results in this series of 45 cases refers to control of shock and is not directly concerned with basic pathologic changes or ultimate outcome of surgical conditions. It is also agreed that some of the patients in mild and moderate shock would no doubt have responded to less effective measures alone. Nevertheless, because of the element of uncer-

tainty in any case of shock, the most efficient available therapy should always be employed.

Where hemorrhage was a large or even a dominant factor in shock, concentrated plasma was found to be so effective and rapid in action that it was used not merely as a blood substitute but as a definite addition and improvement to the use of whole blood. Three cases of our series are reported in some detail to illustrate



the typical response to hypertonic plasma therapy. Case 1 is typical of the shock seen in hospital operative cases, case 3 illustrates the treatment of shock when the hemoglobin content approaches the critical level, and case 16 is due principally to exsanguinating hemorrhage.

CASE 1.—A white woman aged 46 passed into profound shock shortly after a vaginal hysterectomy. At operation the anesthetic was considered satisfactory and no excessive blood loss was noted. She was cold and clammy, sweating profusely and tossing restlessly. The heart tones were faint and weak, while the blood pressure and pulse were imperceptible in either arm. In view of her grave condition 100 cc. of hypertonic (four times) plasma was given intravenously in one minute. The sweating diminished and the patient improved, but since the pulse and blood pressure could not be obtained an additional 100 cc. of the plasma was rapidly given five minutes later. Immediately the radial pulse became palpable and perspiration ceased. The rapid rise in blood pressure to 92 systolic and 84 diastolic at ten minutes, and 102 systolic and 78 diastolic at one hour is seen in chart 1. The pulse simultaneously improved to 112 and then 104 at one hour. The shock was considered under control and at this time 500 cc. of citrated blood was started intravenously because of a lowered hemoglobin. Satisfactory progress continued thereafter.

CASE 3.—A Negro woman aged 32, a multipara, quintigravida, gave a history of hypertension of two years' standing with recent headaches and convulsive equivalents. The blood pressure was 200 systolic and 130 diastolic on admission. The possibility of a toxemic factor was considered and in two stages the patient was bled 1,000 cc. and given 150 cc. of hypertonic (four times concentrated) plasma. There was no improvement, and a cesarean section was performed. During the operation there was considerable loss of blood followed by deep shock with imperceptible blood pressure in the arms. One hundred cc. of five times concentrated plasma was given rapidly, and in fifteen minutes the blood pressure was 130 systolic and 100 diastolic. However, it gradually decreased and in thirty minutes it was imperceptible. Then 100 cc. of four times concentrated plasma was repeated and the blood pressure in five minutes was 70 systolic and 60 diastolic, in ten minutes 80 systolic and 66 diastolic, but soon dropped to 66 systolic and 58 diastolic. It was assumed that the total circulating hemoglobin content had approached or reached the critical level, and 1,000 cc. of whole blood was given by two portals. Recovery from shock was rapid, as illustrated by chart 2, and three hours after the operation the blood pressure was 130 systolic and 100 diastolic.

CASE 16.—A white man aged 55 was admitted to the emergency service in profound shock. He had been found in a pool of blood following multiple lacerations of the neck. On admission he was comatose, cold, cyanotic, clammy and sweating profusely. The respirations were irregular and gasping, and the pulse and blood pressure could not be obtained. It was impossible to obtain a drop of blood from the fingertip. Shortly after admission 100 cc. of concentrated plasma was rapidly given intravenously. During the administration of the last 50 cc. the patient began to move and mumble. Sweating ceased abruptly. Within fifteen minutes the pulse was palpable and the patient, though irrational, was talking. A second dose of 50 cc. was given thirty minutes after the first, and 500 cc. of citrated blood from the bank was started intravenously. A third dose of 50 cc. of plasma was given when about 200 cc. of blood had been administered. Chart 3 shows the steady rise in blood pressure of 70 systolic and 50 diastolic at five minutes to 84 systolic and 54 diastolic at one hour. One hour and twenty minutes after the third dose, the blood pressure was 110 systolic and 70 diastolic and the pulse was 100. The following day an emergency tracheotomy was followed by a dose of 50 cc. of four times concentrated plasma with a rise in blood pressure to 90 systolic and 50 diastolic. From then on improvement continued and the patient was discharged recovered.

#### COMMENT

As illustrated in the cases of shock herein reported, the effect of hypertonic plasma on shock is, in general, an almost invariable, immediate, marked and sustained

increase in blood pressure. Other shock phenomena also show dramatic changes. Sweating, for example, may cease entirely before all of a dose of plasma is given, while return to consciousness from coma often occurs in a few minutes.

While there is some reason to believe that the extreme speed of response may be due in part to direct stimulation of the vascular system, there is also direct laboratory evidence of a remarkably early increase in circulating volume. The decrease in whole blood specific gravity, hematocrit, red cell count and hemoglobin content indicate a definite increase in plasma volume. That this increase in volume is due in large measure to withdrawal of tissue fluid into the circulation and not merely to the added volume of concentrated plasma is shown by (a) decrease of whole blood specific gravity, although the specific gravity of the added concentrated plasma was much greater than that of whole blood, (b) relatively little change in the specific gravity of the patient's plasma, occasionally a decrease, and (c) extent of the change in plasma volume, as shown by hematocrit or hemoglobin being out of proportion to the amount given. These evidences of increased plasma volume and fluid shifts can be found early, in fact immediately after the administration of plasma is completed.

This extreme speed of fluid shift is important in view of the rapidity with which large quantities of protein can be introduced into the circulation. The total effects of these changes are diametrically opposed to the mechanism of traumatic shock with its loss of plasma volume into the tissues. It is important to note that the easily utilized interstitial fluid according to Blalock<sup>2</sup> amounts to approximately three times the total volume of blood plasma in a normally hydrated person. This indicates that this source of fluid should be adequate except in severely dehydrated patients.

Another point is brought out by Brennan<sup>17</sup> in his demonstration that in shock red cells apparently take up water, increasing as much as 50 per cent in size. Hypertonic plasma should be superior to whole plasma in reducing erythrocyte size by water shift. Removal of fluid from abnormal locations seems preferable to mere addition of fluid to the circulation, since such misplaced fluid may be deleterious to capillary, tissue and red cell function. While critical statistical evaluation in clinical cases of this type is impossible, the definite impression is obtained that the scope of treatment of shock is extended to include cases otherwise unresponsive. In the treatment of severe posthemorrhagic shock, hypertonic plasma, followed by whole blood transfusion, has a definite place. As Blalock<sup>2</sup> has shown, transfusion of even greater amounts of blood than that lost by hemorrhage may not restore adequate circulation, particularly when the shock is severe and prolonged. In our clinical cases of this type there are indications that hypertonic plasma, by immediately accelerating the circulation, may yield beneficial results where whole blood alone might fail. We wish to emphasize that this stimulating effect seems to depend on the concentration and speed of administration possible by this type of plasma only. Consequently, even when unlimited quantities of blood are available, we recommend that hypertonic plasma be given.

When the loss of red cells reaches or exceeds the critical amount of 60 to 75 per cent lost, no amount of plasma alone will suffice and whole blood must be added for any permanent good result. However, with less

severe hemorrhage, concentrated plasma may be used as a blood substitute to good advantage. Put up in dry lyophilic form, accompanied with enough pyrogen-free water to make the four times concentrate, it has many points of superiority over whole plasma. For military use in particular, the smaller bulk, perfect storage, simplicity of giving by syringe, speed of administration and rapidity of therapeutic action recommend it.

Reactions have not been a serious problem in the Baylor University Hospital plasma service. Only three febrile reactions were encountered in two hundred and ninety-nine administrations of concentrated plasma, a reaction rate of only 1.003 per cent. In 1 case unsuitable pyrogenic water was added by mistake, and in the second instance the patient in hemolytic crisis was having chills and fever at irregular times. The third patient had a febrile reaction of the type caused by pyrogenic substances, although the specific error in technic was not found. In the entire series two transient urticarial reactions were seen. The low reaction rate is attributed to the use of strictly pyrogen-free water in preparing the concentrate, and to avoidance through proper desiccation of any possible denaturation of protein, deterioration in storage, precipitation of fibrin or failure of complete solution. Furthermore, no untoward effects from either increased potassium or sodium content due in part to concentration were ever observed.

A tendency toward carpopedal spasm was noted with massive doses in 2 children. One of these had previously had spontaneous spasm of this type. Intravenous calcium chloride immediately relieved this tendency, suggesting that the patient's ionic calcium might have been temporarily reduced, owing to union with the excess of sodium citrate in the plasma. For use in pediatrics, serum might therefore be preferred to plasma. In our experience with small amounts of serum there were no febrile reactions. We agree with Levinson<sup>15</sup> that in this respect it is immaterial whether serum or plasma is used.

Occasionally the patient complained of dull and vague aches along the course of veins receiving the plasma. This has invariably ceased after administration has been completed. Complaint was also registered when hypertonic plasma was inadvertently given into tissues, but the discomfort was of short duration and without after-effects.

Hypertonic plasma, like most potent therapeutic agents, can be somewhat dangerous if misused. Unless preliminary bleeding of more than four times the volume to be given is done, its use in congestive heart failure is definitely contraindicated. One instance of increased blood volume with pulmonary edema after plasma administration was encountered but was promptly relieved by phlebotomy. However, a small dose of concentrate after proper bleeding gives excellent results in pulmonary edema.

The doses of four times concentrated plasma used in our cases have frequently been larger than heretofore recommended. In shock the aim should be to supply at least 40 per cent of blood volume lost. This might require from 200 to 300 cc. for an average adult in deep shock. In actual use as little as 100 cc. usually suffices and may be repeated as required. However, since speed is important it is advisable in profound shock to give larger initial amounts of 150 to 200 cc. In hypoproteinemic states significant or dangerous increase of blood volume and raising of plasma protein levels following the administration of concentrated

plasma may not occur because of the sponglike effect of depleted storage depots for plasma proteins. This rapid removal of plasma proteins, as described by Madden and Whipple,<sup>9</sup> has been observed in some cases. For example a dose of 200 cc. of four times concentrated plasma given in forty minutes to an edematous 48 pound (22 Kg.) child with nephrosis resulted in only transient and slight rise in blood pressure and an increase in plasma proteins not commensurate with the amount given. Subsequent large doses did raise and sustain these protein levels.

The use of laboratory tests in the study of early changes and course of shock was somewhat disappointing. This was true particularly when hemorrhage was a factor and hemoconcentration could not be used as a reliable criterion of shock. When hemoconcentration was definite and capillary changes were foremost in pathogenesis, these laboratory tests were of definite value in predicting and following blood volume changes. For this purpose we found the photoelectric hemoglobin estimation the most satisfactory of all the tests used.

#### CONCLUSIONS

On the basis of clinical results in 45 closely followed cases of shock, intravenous hypertonic plasma is advocated as the treatment of choice in shock.

The safety of this form of therapy is reflected in the low febrile reaction rate of 1.003 per cent among 299 administrations of concentrated plasma.

### Clinical Notes, Suggestions and New Instruments

#### BACTEROIDES SEPTICEMIA REPORT OF A CASE WITH RECOVERY

ALEX E. BROWN, M.D.; HENRY L. WILLIAMS, M.D., AND  
WALLACE E. HERRELL, M.D., ROCHESTER, MINN.

Infections caused by bacteria of the genus *Bacteroides*, judged by our experience and by reports in the literature, are extremely rare, and, judged by the same criteria, cases of *Bacteroides septicemia* are still less frequently encountered. In a review by E. C. Rosenow Jr. and one of us<sup>1</sup> of 144 cases of septicemia with positive blood culture, exclusive of cases of subacute bacterial endocarditis associated with *Streptococcus viridans*, seen at the Mayo Clinic in the years 1934 to 1936 inclusive, *Bacteroides* was found to have been cultured from the blood stream in only 6 instances. In a later similar review by two of us<sup>2</sup> of 174 cases of septicemia with positive blood culture encountered in the three year period from 1937 to 1939 inclusive, *Bacteroides* was found as the causative organism in only 8 cases. In all of the foregoing instances as well as in 2 cases of *Bacteroides septicemia* reported by Thompson and Beaver<sup>3</sup> in 1932 the disease was fatal. Much credit must be given to the last mentioned authors for their stimulating studies and contributions on this subject, some of which were made in cooperation with Henthorne and Macy.<sup>4</sup> In 10 cases of *Bacteroides* with probable positive blood culture which Thompson and Beaver collected from the literature, recovery was

From the Division of Medicine (Dr. Brown and Dr. Herrell) and the Section on Otolaryngology and Rhinology (Dr. Williams), the Mayo Clinic.

1. Rosenow, E. C., Jr., and Brown, A. E.: *Septicemia: A Review of Cases, 1934-1936, Inclusive*, Proc. Staff Meet., Mayo Clin. 13: 89-93 (Feb. 9) 1938.

2. Herrell, W. E., and Brown, A. E.: *The Treatment of Septicemia: Results Before and Since the Advent of Sulfamido Compounds*, J. A. M. A., to be published.

3. Thompson, Luther, and Beaver, D. C.: *Bacteremia Due to Anaerobic Gram-Negative Organisms of the Genus Bacteroides*, M. Clin. North America 15: 1611-1626 (May) 1932.

4. Beaver, D. C.; Henthorne, J. C., and Macy, J. W.: *Abscesses of the Liver Caused by Bacteroides Funduliformis*, Arch. Path. 17: 493-509 (April) 1934.

noted in only 4. In 6 cases of *Bacteroides* infection reported by Dixon and Deuterman<sup>5</sup> in 1937 in which the infection followed operation for carcinoma of the large intestine, recovery occurred in only one and a positive blood culture was not obtained in this instance.

The generic name *Bacteroides* was given by Castellani and Chambers<sup>6</sup> in 1919 to a group of bacteria which have been recorded by Bergey<sup>7</sup> as obligate, rod-shaped, non-spore forming anaerobes with variable motility and gram-staining characteristics. Henthorne, Thompson and Beaver<sup>8</sup> have described *Bacteroides funduliformis* and *fragilis* as the gram-negative organisms of the genus *Bacteroides* and mention the existence of *Bacteroides ramosus* as the gram-positive bacterium. According to these authors "strict anaerobes which may be classified in the genus *Bacteroides* have been isolated from fetid and gangrenous suppurations of practically all organ systems of the human being, as well as from normal mucous membranes." In our experience infections caused by *Bacteroides* have occurred principally as complicating factors in the wake of serious debilitating primary disease.

The case of *Bacteroides* septicemia which we are reporting at this time is the only one of this type at the Mayo Clinic in which we have known recovery to occur. In addition to the culturing of *Bacteroides* from the blood stream of the patient it was also identified in sputum resulting from a complicating pneumonia.

Cohen,<sup>9</sup> in a review of the literature and original research study in 1932, reported on the importance of anaerobic organisms in abscesses of the lungs. In the light of the development of distinct jaundice in this case it is of additional interest that Beaver, Henthorne and Macy have reported 2 cases of sepsis caused by *Bacteroides funduliformis* and associated with hepatic abscess. Henthorne and Macy with Thompson also have stressed the frequency with which abscesses of the lungs and joints are produced by *Bacteroides*.

#### REPORT OF CASE

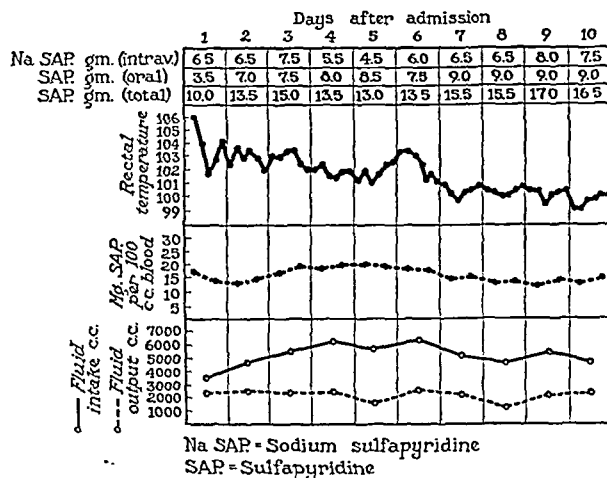
A man aged 24 was admitted to the hospital in an extremely toxic condition and with a temperature of 106 F. He stated that tonsillitis had developed a week previously and that three days later an attempt had been made to incise a supposed peritonsillar abscess on the right. Soon after this a temperature up to 106 F. developed. On examination a necrotic ulcer was noted in the right supratonsillar region, the right tonsil was swollen and the submaxillary and the subangular groups of cervical lymph nodes were swollen and tender. Palpation anterior to the border of the sternocleidomastoid muscle revealed that the internal jugular vein was exquisitely tender from the styloid process to the clavicle. A diagnosis of thrombophlebitis of the internal jugular vein with septicemia secondary to necrotic pharyngitis was made. The patient was given sulfanilamide on the supposition that the hemolytic streptococcus was the causative organism. Section and excision of the right internal jugular vein were considered but it was thought that the extremely critical condition of the patient contraindicated surgical intervention. At this time the urine contained albumin grade 2, casts grade 2 and erythrocytes grade 2 to 3 (on a grading basis of 1 to 4). Sulfanilamide 10.6 Gm. (159 grains) was given orally to the patient in the first thirty-six hours following admission and produced a concentration of 8 mg. of sulfanilamide per hundred cubic centimeters of blood.

Besides the complication in the throat, bilateral bronchopneumonia and jaundice developed three days after admission. On

the fifth day after admission the serum bilirubin was 13.6 mg. per hundred cubic centimeters and the van den Bergh reaction was direct. The results of urinalysis persisted as previously noted.

The initial cultures which were made from the throat were negative for hemolytic streptococci, and cultures from the blood were also negative for these organisms at the end of forty-eight hours. We felt that on the basis of the foregoing observations it was quite possible that some other organism than the hemolytic streptococcus might be the cause of the existing infection and therefore we decided to use sulfapyridine in preference to sulfanilamide. This decision was based on the fact that sulfapyridine appears to possess greater therapeutic activity against a wider range of organisms than sulfanilamide possesses and is therefore the drug of choice in infections produced by unknown organisms and the additional fact that little or no clinical improvement had been produced by sulfanilamide. It is of interest and characteristic of cultures for *Bacteroides* that the blood culture which was negative at the end of forty-eight hours was positive for *Bacteroides funduliformis* at the end of eight days.

After the decision was made to use sulfapyridine in preference to sulfanilamide we immediately proceeded to establish and



Course and treatment with sulfapyridine.

maintain a high concentration of sulfapyridine in the blood (from 16 to 18 mg. per hundred cubic centimeters) in accordance with our established plan for treatment of meningitis, septicemia and fulminant infections. The response to this type of treatment was immediate. Constant gradual improvement occurred in the patient's condition and the temperature by rectum declined from 106 to 100 F. at the end of eight days. By this time too the urine had returned to normal and no longer contained albumin, blood or casts. The jaundice gradually subsided and at the end of twenty-one days the level of the serum bilirubin had returned to normal. Improvement also was noted in the pneumonia, and the rectal temperature remained at about 100 F. until the thirtieth day after admission, when signs of pleurisy on the left side developed and the temperature gradually increased to reach 103 F. daily. On the thirty-second day culture of the sputum disclosed *Bacteroides*. The septic type of temperature persisted and after thoracentesis Dr. Harrington on the forty-seventh day performed an open operation with resection of the eighth and ninth ribs and evacuation of 2,000 cc. of pus from the left pleural cavity. The temperature returned to normal shortly after this procedure and remained normal thereafter.

The long schedule of treatment necessitated by the persistence of infection makes it advisable to summarize the therapeutic plan of procedure in order to conserve space. From the standpoint of chemotherapy it was necessary in order to obtain the desired concentration of 16 to 18 mg. of the drug in 100 cc.

5. Dixon, C. F., and Deuterman, J. L.: Postoperative *Bacteroides* Infection: Report of Six Cases, *J. A. M. A.* 105: 181-185 (Jan. 16) 1937.

6. Castellani, Aldo, and Chambers, A. J.: *Manual of Tropical Medicine*, ed. 3, New York, William Wood & Co., 1919.

7. Bergey, D. H.: *Bergey's Manual of Determinative Bacteriology: A Key for the Identification of Organisms of the Class Schizomycetes*, Baltimore, Williams & Wilkins Company, 1934, pp. 404-413; 1939; pp. 556-570.

8. Henthorne, J. C.; Thompson, Luther, and Beaver, D. C.: Gram-Negative Bacilli of the Genus *Bacteroides*, *J. Bact.* 31: 255-274 (March) 1936.

9. Cohen, John: The Bacteriology of Abscess of the Lung and Methods for Its Study, *Arch. Surg.* 24: 171-188 (Feb.) 1932.

of blood to give from 6 to 9 Gm. (90 to 135 grains) of drug daily in six divided doses orally at intervals of four hours. Estimations were made each morning and evening of the concentration of sulfapyridine in the blood, and two supplementary doses of the sodium salt of sulfapyridine were given intravenously daily following the receipt of the reports from the laboratories in order to maintain the concentration that was desired. A total of from 4.5 to 7.5 Gm. (67½ to 112½ grains) of the sodium salt of sulfapyridine was thus given daily in addition to the oral dose of sulfapyridine, so that the total amount of sulfapyridine given in each twenty-four hours varied from 13 to 15.5 Gm. (195 to 232½ grains).

The plan of procedure for the first ten days of treatment is given in the chart.

The doses just cited served to maintain the concentration of sulfapyridine at between 14 and 19 mg. per hundred cubic centimeters of blood for the first eleven days of treatment; subsequently the concentration was decreased gradually to from 8 to 9 mg. per hundred cubic centimeters of blood and was maintained at this level during the remainder of the twenty-nine days of chemotherapy.

A total amount of 347 Gm. (5,205 grains) of sulfapyridine was given over a period of twenty-nine days and of this amount 230.5 Gm. (3,457½ grains) was given orally and 116.5 Gm. (1,747½ grains) of the sodium salt was given intravenously. These doses constitute the largest daily and total doses of sulfapyridine that we have ever used but were necessary in order to maintain the desired concentration of the drug in the blood because of the high daily level of intake and output of fluid. The patient was in an exceedingly toxemic state and he craved large amounts of fluid, so that, contrary to our usual plan of maintaining an approximate intake of 3,000 cc. of fluid and an output of 1,500 cc., in this instance no particular effort was made to limit fluids as long as it was possible to maintain the desired concentration of drug in the blood. In the light of our previous experience with septicemia and with *Bacteroides* septicemia in particular we believed that treatment was necessary as long as fever persisted and as long as the threat of the pulmonary or hepatic abscesses persisted in addition to the known complication of empyema. We also believed that this large intake of fluid possibly might be a vital factor in protecting the kidney from complications from the prolonged use of large amounts of sulfapyridine. The patient received oxygen therapy for his first two weeks in the hospital.

Aside from some tendency to mild anemia there was a comparative absence of toxic manifestations from the drug. Nausea and some abdominal distress were present at times late in the course of the treatment and we felt that these symptoms existed as manifestations of toxicity of the drug. The tendency to anemia was probably due in part to the use of sulfapyridine, but the sepsis was probably the most important factor in its production. We have always felt that it is advisable to use frequent small transfusions of blood in the presence of septicemia and that blood transfusions are also indicated when anemia is present in addition and when active chemotherapy is being carried on. Owing to the fact that the patient had an apparent inexhaustible supply of available blood from donor friends it was possible to give him an unusually large number of transfusions of blood. Transfusions averaging 300 cc. of blood were given daily for the first thirty-four days of treatment and a total of forty transfusions was given throughout the illness. Through the use of this measure the number of erythrocytes did not drop below 3,100,000 per cubic millimeter of blood and was generally maintained at about 4,000,000.

#### COMMENT AND SUMMARY

This case represents the first instance of *Bacteroides* septicemia at the Mayo Clinic in which recovery is known to have occurred. One reason that this case is of particular interest is that sulfapyridine was administered. Heretofore, the sulfamido compounds have been considered not to be particularly effective against anaerobic organisms. Contrary to our usual experience, the infection was primary in nature and not superimposed on a chronic disease process.

Recovery occurred in spite of the fact that the *Bacteroides* septicemia was complicated by hepatitis and possibly liver abscess with jaundice; toxic, hemorrhagic, focal (?) nephritis; bilateral bronchopneumonia; left empyema, and cellulitis with thrombosis of the right internal jugular vein.

A total of 347 Gm. (5,205 grains) of sulfapyridine was given in twenty-nine days without the occurrence of serious toxic complications from the drug. Of the amount of sulfapyridine administered, 230.5 Gm. (3,457½ grains) was given orally and 116.5 Gm. (1,747½ grains) of the sodium salt was given intravenously.

This case illustrates well the principle that the important factor in treatment from the standpoint of chemotherapy is the maintenance of satisfactory concentrations of drug in the blood irrespective of the daily doses of drug necessary to maintain these desired concentrations.

Frequent transfusions and a high intake and output of fluid are undoubtedly factors of importance in the presence of septicemia in the prevention of complications when large doses of the sulfamido drugs are employed. We realize, of course, that in certain instances it may be advisable to give less fluid and therefore less drug than was given in this case in order to maintain the concentrations of drug desired in the blood.

#### DELAYED APPEARANCE OF REACTION TO ELASTIC GLASS WRIST WATCH STRAP

W. W. BAUER, M.D., CHICAGO

A physician aged 48 with a history of autumnal hay fever since age 3 and gastric intestinal sensitivity to most of the cabbage family and attacks of severe headaches, sometimes of the migraine type, after the eating of cabbage and other vegetables in the same group, suffered a severe dermatitis from the wearing of a watch bracelet of the new synthetic, flexible, glass-like substance sold under various trade names. The onset of the symptoms was delayed two months after the purchase of the watch bracelet, although it was worn daily on the left wrist. The first manifestation was itching and erythema, followed in about twelve hours with typical urticarial wheals. These were found around the entire wrist except in the area under the watch itself. Although the first symptoms, itching and erythema, affected the entire area of skin with which the watch bracelet was in contact, the eruption at the end of twenty-four hours was in two definite lines, coinciding with the stitching of the bracelet. The stage of urticaria was followed in about forty-eight hours by extensive vesiculation with continuance of violent itching. The vesicles began subsiding at the end of five days without rupture, leaving an area of slightly raised induration. This area could be partially blanched on pressure or by putting the skin under slight tension, but even so there remained a definite evidence of inflammatory changes in the tissues.

On the appearance of the first symptoms, the watch was removed and placed on the other wrist for four hours to see what would happen. The same process was repeated on the other wrist to a somewhat more limited extent due probably to the shorter period of contact. On the right wrist there was less vesiculation but more induration.

The patient suffered in January 1940 from a generalized dermatitis attributed by a process of elimination to a newly purchased suit of cotton pajamas. Patch tests verified the etiologic significance of the pajamas. The patient also gave a history of having suffered a severe dermatitis involving both ankles immediately after the purchase and the first wearing of a new pair of socks.

The significant feature of this watch bracelet dermatitis is that sensitivity developed suddenly after the watch bracelet had been worn continuously for two months. The only significant precipitating factor which could be suggested is that dermatitis developed at a time when the patient spent four hours in conference in an excessively hot room and perspired rather freely.

535 North Dearborn Street.

## Special Article

### GLANDULAR PHYSIOLOGY AND THERAPY

#### PHYSIOLOGY OF THE OVARIES

EDGAR ALLEN, PH.D.

NEW HAVEN, CONN.

*This special article is published under the auspices of the Council on Pharmacy and Chemistry. It is one of a series which will be published in book form as the second edition of "Glandular Physiology and Therapy." The opinions expressed in this article are those of the author and do not necessarily represent the official views of the Council.—Ed.*

There are several important points about the ovaries which have emerged clearly under experimental attack. Once clearly defined, in many cases accentuated through experimental conditions, some of the phenomena stand out as normal in certain species but occur in others only occasionally. An instance is the formation of corpora lutea (accessory ones) in large follicles that have not ovulated. The ova are trapped inside, but the cells of the follicle take on luteal characteristics. Known for many years, this condition was first induced experimentally by unbalanced stimulation of the ovaries with anterior pituitary extracts.<sup>1</sup> It appears normally in the pregnant mare<sup>2</sup> and the pregnant porcupine<sup>3</sup> and occasionally in the nonpregnant monkey.<sup>4</sup> More careful observations may establish this as an occasional occurrence in women!

Another instance is the extreme development of the theca folliculi, the zone immediately surrounding the basement membrane about the outer layer of follicle cells, as described in the ovary of the pocket gopher by Mossman.<sup>5</sup> Although this tissue develops to a certain extent around growing follicles in the ovaries of most mammals, in the gopher it reaches extremes and apparently has an important secretory function accessory to that of the follicle, for it develops at puberty, when the symphysis pubis in this animal is resorbed to enlarge the birth canal. This resorption has

been produced experimentally in males as well as in females, both gophers<sup>6</sup> and mice,<sup>7</sup> by injecting estrogen.

Another important point, which may now be mentioned as a fact rather than as an interesting possibility, is that a group of follicles, instead of just one, begins rapid growth which may result in ovulation of only one egg (or a few eggs in litter-bearing animals), the other follicles undergoing atresia and being resorbed. Loeb<sup>8</sup> emphasized this condition in his early studies of the guinea pig. It apparently needs the mass action of a group of follicles to assure ovulation of one (or a few), and this is apparently concerned with the secretory function of the follicles. The experiments of Hohlweg<sup>9</sup> and of Westman<sup>10</sup> are cited in this connection. Hohlweg reported precocious ovulation and the formation of corpus luteum following injections of estrogen in immature rats. Westman succeeded in destroying all of one ovary except one growing follicle. This was done in the rabbit by means of a fine diathermy needle. The other ovary was then removed. The lone remaining follicle was unable to proceed through normal development. If, however, a single dose of estrogen was given at the time of the operation, this lone follicle did develop normally and ovulate. Later this experiment was repeated in hypophysectomized animals.<sup>11</sup> This investigation assigns a supportive secretory function (estrogenic) to other follicles than the favored ones, i. e., to the ones which develop only partially, and then die and are eliminated. The "favored follicle" truly "stands upon the shoulders of its contemporaries."

In a similar way it may be inferred that the partly developing follicles probably secrete estrogen, which provides a necessary supporting action for the formation and function of corpora lutea. This, too, has been tested by injecting estrogen and found to be true.<sup>12</sup> In fact, injections of estrogen prevent the rapid involution of the corpora lutea which follows removal of both (1) the anterior lobe of the pituitary<sup>13</sup> and (2) the pregnant uterus with its embryos and placenta.<sup>14</sup> The latter evidence may mean that pituitary support of luteal function is partly through a stimulus to follicular production of estrogen rather than entirely through a specific "luteinizer." The support of luteal function by estrogen is in line with Willard Allen's observation<sup>15</sup> that progesterone and estrogen together were more effective in producing progestational changes in the uterus than was progesterone alone.

From the Department of Anatomy, Yale University School of Medicine.

Since the outline for the second edition includes "The Estrogenic Substance" by Dr. Doisy, "Corpus Luteum Hormone" by Dr. Corner, and "Menstruation" by Dr. Bartelmez, this chapter on "The Physiology of the Ovaries" is designed as general in nature. An attempt is made to reunite considerations of the production of both eggs and hormones. W. U. Gardner and C. A. Pfeiffer have contributed criticisms and suggestions for improvement. Limitations as to length prevent inclusion of several important aspects of ovarian physiology. Many additional references will be found in: Allen, E.; Danforth, C. H., and Doisy, E. A.: *Sex and Internal Secretions*, edition 2, 1939.

1. Evans, H. M.; Meyer, Karl; Simpson, M. E.; Szarka, A. J.; Pencharz, R. L.; Cornish, R. E., and Reichert, F. L.: The Growth and Gonad-Stimulating Hormones of the Anterior Hypophysis, in *Memoirs of the University of California, Berkeley, Calif., University of California Press*, 1933, vol. 11, pp. 144-6. Evans, H. M., and Long, J. A.: Characteristic Effects upon Growth, Oestrus, and Ovulation Induced by the Intraperitoneal Administration of Fresh Anterior Hypophyseal Substance, *Anat. Rec.* 23: 19 (Jan.) 1922. Engle, E. T., and Smith, P. E.: The Origin of the Corpus Luteum in the Rat as Indicated by Studies upon the Luteinization of the Cystic Follicle, *ibid.* 43: 239 (Aug.) 1929. Feudt, H. L.; Hisaw, F. L., and Leonard, S. L.: The Gonad-Stimulating and the Luteinizing Hormones of the Anterior Lobe of the Hypophysis, *Am. J. Physiol.* 97: 291 (May) 1931. Van Dyke, H. B., and Wallen-Lawrence, Zonia: Further Observations on the Gonad-Stimulating Principle of the Anterior Lobe of the Pituitary Body, *J. Pharmacol. & Exper. Therap.* 47: 163 (Feb.) 1933.

2. Cole, H. H.; Howell, C. E., and Hart, G. H.: The Changes Occurring in the Ovary of the Mare During Pregnancy, *Anat. Rec.* 49: 199 (May) 1931.

3. Mossman, H. W.: The Ovarian Cycle in the Porcupine, *Erethizon dorsatus*, with Particular Regard to the Natural Occurrence of Unilateral Luteinization of Unruptured Follicles, *Anat. Rec.* 76 (supp. 2): 44 (Feb.) 1940.

4. Corner, G. W.: Accessory Corpora Lutea in the Ovary of the Monkey, *Macacus Rhesus*, *Anat. Rec.* 76 (supp. 2): 16 (Feb.) 1940.

5. Mossman, H. W.: The Thecal Gland and Its Relation to the Reproductive Cycle: A Study of the Cyclic Changes in the Ovary of the Pocket Gopher, *Geomys Bursarius* (Shaw), *Am. J. Anat.* 61: 289 (July) 1937.

6. Hisaw, F. L.: The Influence of the Ovary on the Resorption of the Pubic Bones of the Pocket Gopher, *Geomys Bursarius*, *J. Exper. Zool.* 42: 411, 1925.

7. Gardner, W. U.: Pelvic Changes Occurring in Male Mice Receiving Large Amounts of Folliculin Benzoate, *Proc. Soc. Exper. Biol. & Med.* 33: 104, 1935.

8. Loeb, L.: Ueber die Bedeutung des Corpus luteum für die Periodizität des sexuellen Zyklus beim weiblichen Säugetierorganismus, *Deutsche med. Wchnschr.* 37: 17, 1911.

9. Hohlweg, W.: Veränderungen des Hypophysenvorderlappens und des Ovariums nach Behandlung mit grossen Dosen von Follikelhormon, *Klin. Wchnschr.* 13: 92 (Jan. 20) 1934.

10. Westman, A.: Untersuchungen über die Abhängigkeit der Funktion des Corpus luteum von den Ovarialfollikeln und über die Bildungsstätte der Hormone im Ovarium, *Arch. f. Gynäk.* 158: 476, 1934.

11. Westman, A., and Jacobsohn, D.: Experimentelle Untersuchungen über die Bedeutung des Hypophysen-Zwischenhirnsystems für die Produktion gonadotroper Hormone des Hypophysenvorderlappens, *Acta obst. et gynec. Scandinav.* 17: 235, 1937.

12. Westman, A., and Jacobsohn, D.: Ueber Oestrinwirkungen auf die Corpus luteum-Funktion, *Acta obst. et gynec. Scandinav.* 17: 1 and 13, 1937. Heckel, G. P., and Allen, W. M.: Maintenance of the Corpus Luteum and Inhibition of Parturition in the Rabbit by Injection of Estrogenic Hormone, *Endocrinology* 24: 137 (Feb.) 1939.

13. Robson, J. M.: Maintenance by Oestrin of the Luteal Function in Hypophysectomized Rabbits, *J. Physiol.* 90: 435 (Sept.) 1937.

14. Greep, R. O.: Changes in the Corpora Lutea of Rabbits Following Hysterectomy During Pregnancy, *Anat. Rec.* 76 (supp. 2): 25 (Feb.) 1940.

15. Allen, W. M., and Heckel, G. P.: The Effect of Continued Injections of Progesterin and Combinations of Oestrin and Progesterin on the Endometrium of the Castrated Rabbit, *Anat. Rec.* 61 (supp. 3): 2 (March) 1936.

This synergism seems to occur in both ovarian and uterine functions.

That such an influence may be felt more strongly locally than systemically, i. e., in the same ovary more than in the other ovary (to which the stimulus must be carried by the blood stream), is shown by Mossman's<sup>3</sup> description of conditions during pregnancy in the porcupine. The porcupine bears only one young at a time and therefore usually ovulates only one ovum. However, several other follicles succeed in reaching large size. When the favored follicle ovulates, these others are transformed into accessory corpora lutea, similar in all respects to the true corpus except that they have the ova trapped inside. So far this is similar to conditions in the pregnant mare<sup>2</sup> and to Corner's<sup>4</sup> observations in the ovaries of 4 of 23 nonpregnant monkeys killed between ovulation and the end of menstruation. But the remarkable thing about the porcupine is that as pregnancy progresses the accessory corpora in the ovary which ovulated, and therefore the one which contains the true corpus, persist throughout pregnancy, while those in the other ovary disintegrate before midgestation.<sup>10</sup> This might be explained on the basis of a strong hormonal influence establishing the luteinization but diminishing as gestation progresses until some local influence from the true corpus sustains structures in that ovary but fails to reach systemically to sustain those in the other ovary.

During recent years while the endocrinology of reproduction has been making such rapid advances,<sup>17</sup> there has been a tendency to discuss ovarian hormones apart from other phases of ovarian physiology. However, the production of eggs is still the primary function of the ovaries. Phylogenetically, this was the first ovarian function, and it is probably still the only function of the ovaries in some of the lower forms. The production of eggs in the mammalian ovary must involve slow but continuous shifting of transient structures of changing size—many follicles forming, growing and dying as a few mature, ovulate and are transformed into corpora lutea. The corpora in turn function for brief periods, depending to some extent on the fate of the eggs previously ovulated from the follicles that nurture them, before they shrink and disintegrate. Therefore, as far as egg production is concerned, the ovary might be compared to "a slowly boiling kettle" in which bubbles (follicles) are forming—from the surface, not from the bottom—sinking in as they grow to medium size, then reversing direction as they enlarge to rupture the surface at ovulation. But, as in any population, many follicles die before maturity; the mortality among ovarian eggs is very great.<sup>18</sup> In fact, this mortality is probably greater than formerly calculated, because new generations of eggs are differentiating from indifferent cells, during sexual maturity,<sup>19</sup> just as new sperm are continuously

formed in the testes. This makes even more important the "selective elimination" to which growing eggs are subjected in the ovaries. These ova are eliminated not so much because they are defective as because there is only a limited supply of necessities, including anterior pituitary gonadotropic hormone, which is essential for their late growth. Many ova which would otherwise die can be brought to multiple ovulation by increased pituitary stimulation.<sup>20</sup> This is probably the key to the remarkable regenerative capacity of the ovary after removal of all but small parts<sup>21</sup> and to the compensatory hypertrophy of one ovary after removal of the other.

One important conclusion which follows is that the life span of ova in mammalian ovaries is usually a short one—in some of the small mammals it may be a matter of two or three weeks—almost as short as that of red blood corpuscles.<sup>10b</sup> This extensive development of transient structures involves constant rebuilding of the vascular nets of growing follicles and then further remodeling when these undergo atresia or ovulate to form corpora lutea.

To produce eggs in a majority of animals, especially birds, storage of nutriment seems necessary; therefore the ovaries must mobilize food for developing eggs. It seems probable that this must be done in competition with other bodily needs for nutriment in both growth and repair. In a general sense, this condition is reflected in the attainment of the major part of body growth before attainment of puberty presages mature ovarian function. Later during pregnancy in viviparous animals this competition for necessities between growing eggs in the ovary and bodily needs may be extended to include competition with the growing embryo and fetus, and during lactation, with function of the mammary glands. At first this competition is probably for things nutritional; later it may extend to include competition for extraovarian hormones, such as those of the anterior lobe of the pituitary, which are necessary for both body growth and reproductive function. This condition is accentuated by starvation, malnutrition or rapid growth of genital cancer. This sort of competition between organs or tissues must involve different rates of growth and metabolism, temporarily sustained.

The second function of the ovaries is the production of hormones. That this function is intimately tied up with growth processes is demonstrated by the striking growth of accessory genital organs of the female produced experimentally by injections of estrogen.<sup>22</sup> In fact, the sexual cycles, both estrous and menstrual, are fundamentally recurring waves of growth in the genital tract.<sup>23</sup> The ovarian estrogen is the essential hormone responsible for these cycles in nonpregnant females.<sup>24</sup> The luteal hormone is in a sense supplementary, acting apparently both as synergist and

16. In the pregnant mare the accessory corpora also do not persist throughout pregnancy.

17. Allen, Edgar; Danforth, C. H., and Doisy, E. A.: Sex and Internal Secretions, ed. 2, Baltimore, Williams & Wilkins Company, 1939.

18. Allen, Edgar; Kountz, W. B., and Francis, B. F.: Selective Elimination of Ova in the Adult Ovary, *Am. J. Anat.* 34:445 (Jan.) 1925.

19. (a) Allen, Edgar: Ovogenesis During Sexual Maturity, *Am. J. Anat.* 31:439 (May) 1923. (b) Evans, H. M., and Swezy, O.: Ovogenesis and the Normal Follicular Cycle in Adult Mammalia, in *Memoirs of the University of California*, Berkeley, Calif., University of California Press, 1931, vol. 9, p. 119. Evidence for ovogenesis is clearest in the adult mouse, in which, by use of the colchicine technique, hundreds of dividing cells, the first stage in ovogenesis, can be found at certain times in the estrous cycle (Allen, Edgar, and Creadick, R. N.: Ovogenesis During Sexual Maturity: The First Stage, Mitosis in the Germinal Epithelium, as shown by the Colchicine Technique, *Anat. Rec.* 69: 191 [Sept.] 1937). Further search with improved techniques will, I believe, furnish additional evidence in other mammals for this process, so fundamental in ovarian physiology.

20. Smith, P. E., and Engle, E. T.: Experimental Evidence Regarding the Role of the Anterior Pituitary in the Development and Regulation of the Genital System, *Am. J. Anat.* 40:159 (Nov.) 1927.

21. (a) Lipschütz, Alexander: On Some Fundamental Laws of Ovarian Dynamics, *Biol. Rev.* 2:263 (Jan.) 1927. (b) E. O. Rasmusen: Regeneration in Ligated Ovaries and of the White Rat (*Mus Norvegicus Albinus*), *Anat. Rec.* 54:87 (Sept.) 1932. (c) Van Wageningen, Gertrude, and Morse, A. H.: Personal communication to the author.

22. Allen, Edgar, and Doisy, E. A.: An Ovarian Hormone: Preliminary Report on Its Localization, Extraction and Partial Purification, and Action in Test Animals, *J. A. M. A.* 81:1819 (Sept. 8) 1923.

23. Allen, Edgar; Doisy, E. A.; Francis, B. F.; Gibson, H. V.; Robertson, L. L.; Colgate, C. E.; Kountz, W. B., and Johnston, C. G.: The Hormone of the Ovarian Follicle: Its Localization and Action in Test Animals, and Additional Points Bearing upon the Internal Secretion of the Ovary, *Am. J. Anat.* 34:133 (Sept.) 1924.

24. Allen, Edgar: The Menstrual Cycle of the Monkey, *Macacus Rhesus*: Observations on Normal Animals, the Effects of Removal of the Ovaries and the Effects of Injections of Ovarian and Placental Extracts into the Spayed Animals, *Contrib. Embryol.* (no. 98), 19:1, 1927.



antagonist, with and against the estrogenic hormone, in various reactions. It is now definitely established that the androgenic hormones may also play important supplementary roles in ovarian endocrine function.<sup>25</sup> In fact, the secretion of the ovaries is probably a mixture of estrogens, androgens and progesterone, functioning at minimal levels during relatively quiescent phases of the sexual cycle but with successive generations of follicles and corpora periodically intensifying their function and momentarily modifying and dominating the total hormone output. The final result must depend on the degree of dominance for a while before the balance swings back. This principle apparently involves not only ovarian tissues but also their interactions with other endocrine glands.

Since the blood stream is the common carrier for both nutritional and hormonal supplies, the matter of competition for limited quantities of these substances, amounting actually to a struggle for survival in some instances, seems most fundamental in any concept of ovarian physiology. The developing eggs in the mammalian ovary might truly be considered a crowded population in a life and death struggle for limited amounts of vital necessities, a struggle so severe that only 400 human eggs, of hundreds of thousands, may reach maturity and be ovulated during the reproductive life of the average woman.

Recent thorough studies of the ovaries in the bat by Guthrie and Jeffers<sup>26</sup> give a clear picture of this sort of competition between growing follicles. During the month of September, in this species, all but one of a group of follicles are eliminated as that favored one, "the follicle of ovulation," grows to ovulation size. The inhibition of follicular growth during pregnancy and lactation may also be logically explained by competition for necessary pituitary secretions during this time by dominant uterine and mammary functions. Interrelations of endocrine glands seem best interpreted by inclusion of a concept of balance through competitive utilization of certain limited vital necessities by successively dominant tissues or organs. The rapid growth of mammary cancer may suppress the function of other genital tissues for the same reason.<sup>26a</sup>

The concept seems to take concrete form more readily when the ovary is considered an aggregate, or colony, of transient individuals. As an ontogenic beginning, the primordial germ cells migrate to the genital ridge from the "germ cell crescent" of the embryonic disk of the bird<sup>27</sup> or from the endoderm of the gut of the mammal.<sup>28</sup> If this germ cell migration is successful, the genital ridge differentiates into an ovary or a testis; if the "germ cells" are prevented from reaching the ridge, a "sterile ovary" without ova (or an atypical testis) results and the primordial germ cells fail in establishing themselves as such in other sites.<sup>29</sup> Therefore both the immigrant cells and the genital ridge environment are important in the differentiation of the ovary.<sup>30</sup>

Apparently these primordial immigrants are not the ancestors of the definitive ova, those which ovulate during adult life. However, because of their presence in the embryonic genital ridge, the overlying peritoneal cells divide, and daughter cells from these divisions differentiate into ova and migrate toward the massed primordial ova beneath. With them go sister cells, which become follicle cells—also from the germinal epithelium. The ova do not divide further; the follicle cells do, and as they proliferate they group around the eggs to form the small follicles. Many such groups are formed during embryonic life, but these follicles and their contained ova probably all die and are resorbed before sexual maturity. New generations of ova are added to replace them,<sup>31</sup> the new growth continuing into adult reproductive life.<sup>19a</sup>

Therefore the hereditary characters, the chromosomes, of the eggs which are ovulated are probably not derived from the migrant primordial germ cells but are segregated in the peritoneum overlying the genital ridge. These cells have no chance to express their potentialities in the next generation unless the immigrant cells reach the site of the forming gonad and "beckon them in." This influence, this attraction, local in action, is probably in the nature of a secretion of the germ cells into the tissue fluids. It might be called a hormone if it were blood borne and its effects systemic. Since this influence probably moves by seepage through tissue fluids and is local, it is better classified as an "embryonic inductor" or "organizer." But hormones act similarly, as is shown in numerous endocrine experiments by more intense local than systemic actions.<sup>32</sup> This failure of the migrant primordial germ cells to become the immediate ancestors of the fertilized eggs that become our children does not mean a break in the chromosomal line of descent, for the undifferentiated cells of the germinal epithelium of the ovary are also descended from the same fertilized ovum. It is rather a temporary recognition of cousins while cells of the "true line" remain temporarily in undifferentiated obscurity.

Although the initial impulse of differentiation of sex in the embryo is undoubtedly genetic,<sup>33</sup> and the chromosomes of the primordial germ cells undoubtedly carry the determination of the genital ridge into the ovary or the testis, the further course of sexual differentiation, that of the accessory reproductive organs, seems to be taken over as an endocrine function of the developing gonad. There is evidence that in the female this embryonic ovarian hormone is estrogenic. At this time it is probably produced primarily by the partially growing follicles, for as yet interstitial and thecal tissues are scarcely developed at all, and corpus luteum participation is still far in the future.

Further development of the ovary consists of several successive "showers" or proliferations of cells, either in cords or in discrete masses, to form ova and follicle cells, and perhaps others which are not organized into follicles and which become interstitial cells. One of the earlier "showers," which forms the medulla of the ovary, seems to carry potentialities for testis formation under certain conditions. Later "showers" give rise to the cells of the fetal ovarian cortex. Thus

25. Koeh, F. C.: Biochemistry of Androgens, in Allen, Danforth and Doisy, *chap. 12*.

26. Guthrie, M. J., and Jeffers, K. R.: Growth of Follicles in the Ovaries of the Bat, *Myotis Lucifugus Lucifugus*, *Anat. Rec.* **71**: 477 (Aug.) 1938.

26a. Allen, E., Diddle, A. W., Strong, L. C., Burford, T. H., and Gardner, W. U.: The Estrous Cycles of Mice During Growth of Spontaneous Mammary Tumors and the Effects of Ovarian Follicular and Anterior Pituitary Hormones, *Am. J. Cancer* **25**: 291, 1935.

27. Swift, C. H.: Origin and Early History of the Primordial Germ-Cells in the Chick, *Am. J. Anat.* **15**: 483, 1914.

28. Allen, B. M.: The Embryonic Development of the Ovary and Testis of the Mammals, *Am. J. Anat.* **3**: 89 (June) 1904.

29. Willier, B. H.: Experimentally Produced Sterile Gonads and the Problem of the Origin of Germ Cells in the Chick Embryo, *Anat. Rec.* **70**: 89 (Dec.) 1937.

30. Willier, B. H.: Embryonic Development of Sex, in Allen, Danforth and Doisy, *chap. 13*.

31. Arai, Hayato: On the Postnatal Development of the Ovary (Albino Rat), with Especial Reference to the Number of Ova, *Am. J. Anat.* **27**: 405 (Sept.) 1920.

32. Lyons, W. R., and Templeton, H. J.: Intravaginal Assay of Urinary Estrin, *Proc. Soc. Exper. Biol. & Med.* **33**: 587 (Jan.) 1936.

33. Bridges, C. B.: Cytological and Genetic Basis of Sex, in Allen, Danforth and Doisy, *chap. 2*.

the ovary has potentialities for both sexes.<sup>34</sup> It is now definitely known that ovarian tissue after puberty can secrete androgen under certain experimental conditions,<sup>35</sup> so that ovaries, as well as the adrenal cortex, may be an accessory source of masculinizing hormone in girls and women.

Apparently the genetic determination of sex involves a balance of genes in the chromosomes.<sup>33</sup> If the balance does not tip to a clear decision, sex intergrades may result. Apparently a similar balance exists between the androgenic and the estrogenic output of the gonads of both sexes. Sex intergrades have been produced by upsetting the usual endocrine balance.<sup>36</sup> Injections of androgens and estrogen early in embryonic life seem partly to reverse the sex as determined genetically or to block one potentiality and permit development in the direction of the opposite one. The transition of control by chromosomes to control by hormones needs much further study, but, since the convincing work of Stockard<sup>37</sup> on inheritance of endocrine imbalance in dogs and of Danforth<sup>38</sup> and Witschi<sup>34</sup> on factors determining type and color of plumage in birds, the significance of genic and endocrine dominance in influencing sex is clearly recognized.

When the consideration of embryonic life is extended to the mammal, ovarian hormones from the mother must be considered, for the placenta is by no means an absolute barrier against maternal hormones entering embryonic and fetal circulation.<sup>39</sup> Fortunately, sexual differentiation of the embryo one way or the other occurs fairly early in gestation. Although suppression of gonadal development by injecting hormones of the opposite sex has been accomplished in both directions, it usually must be done early, and higher levels of hormone must be attained than are found normally.<sup>40</sup>

There is now convincing evidence for the secretion of estrogen, progesterone and gonadotropins by placental tissues, and even by the chorion where no placenta is formed, as in the mare.<sup>41</sup> These products secreted during pregnancy are therefore predominantly fetal rather than maternal. In this connection the important point for ovarian physiology is that during pregnancy the endocrine function of the maternal ovaries is apparently "taken over" to a certain extent by the fetal membranes of the placenta. This is certainly true as far as the secretion of estrogen is concerned, for follicles seldom develop beyond the early antrum

stage during pregnancy. In some animals, notably woman<sup>42</sup> and also the mare,<sup>2</sup> the true corpus luteum is no longer essential to the pregnancy after the first third of gestation.

A consideration of the physiology of the ovaries should include discussion of the growth of eggs, including storage of various kinds of yolk, the development and functions of egg membranes, both the fertilization membrane and the zona pellucida, the appearance of the corona radiata, the changes in the zona at the time of maturation and polar body formation, the withdrawal of processes of adjacent follicle cells from pores in the zona as the egg travels down the tube and the final dissolution of the zona in the uterus before implantation and increase in size of the segmenting ovum are possible—the latter being accomplished by shift of the hydrogen ion concentration of the uterine fluid to the acid side. Limitations of space exclude more than bare mention. Reference is made to the recent monograph of Pincus<sup>43</sup> for this phase of the subject.

One outstanding feature in the early growth of the ovum is its increase in size from deposition of yolk—the kind varying greatly with the species. In the pig there is much clear lipid material; or there may be colorless yolk as in the rabbit, monkey or man, or pigmented yolk as in the carnivores. Yolk deposition in birds has been much studied. Precursors of definitive yolk can be stained cytologically by special dyes and their transport through (secretion by) the follicle cells demonstrated.<sup>44</sup>

As the ovum grows and cells multiply by mitotic division to form the follicle about it, all products of egg metabolism, both incoming and outgoing, must pass through these cells, because the blood supply lies beyond the follicular membrane (the basement membrane of the outer layer of follicle cells). At first, in the very small follicle, the limiting membranes between ovum and follicle cells and the basement membrane which separates follicular epithelium from stroma are hardly noticeable. As the follicle grows, they become much more prominent. The former becomes the tough, resistant capsule, the zona pellucida, through which processes from the inner layer of follicle cells extend to make contact with the surface of the ovum.

When the follicle of the mammalian ovary reaches a certain size, the liquor folliculi begins to form as an intercellular secretion. Cell-free liquor folliculi contains estrogen.<sup>23</sup> This is the best evidence that normally follicular cells secrete this hormone. The accumulation of follicular fluid is not necessary for secretion of estrogen, for solid granulosa cell tumors secrete this hormone.<sup>45</sup> The fact that other cells, such as theca, "interstitial" or even luteal cells, may also secrete estrogen does not invalidate this evidence but merely indicates that they also share this secretion. When ova are destroyed by carefully graded, critical doses of roentgen rays,<sup>46</sup> and regenerating nonovular tissue secretes estrogen, these experiments do not disprove

34. Witschi, Emil: Modification of Development of Sex in Lower Vertebrates and in Mammals, in Allen, Danforth and Doisy,<sup>17</sup> chap. 4.

35. Hill, R. T.: Ovaries Secrete Male Hormone: I. Restoration of the Castrate Type of Seminal Vesicle and Prostate Glands to Normal by Grafts of Ovaries in Mice, *Endocrinology* 21: 495 (July) 1937.

36. Willier, B. H.; Gallagher, T. F., and Koch, F. C.: Sex-Modification in the Chick Embryo Resulting from Injections of Male and Female Hormones, *Proc. Nat. Acad. Sci.* 21: 625, 1935. Burns, R. K.: The Effects of Crystalline Sex Hormones on Sex Differentiation in Amblystoma: I. Estrone, *Anat. Rec.* 71: 447 (Aug.) 1938. Humphrey, R. R.: Studies on Sex Reversal in Amblystoma: III. Transformation of the Ovary of A. Tigrinum into a Functional Testis through the Influence of a Testis Resident in the Same Animal, *J. Exper. Zool.* 58: 333, 1931.

37. Stockard, C. R.: The Physical Basis of Personality, New York, Norton & Company, 1931.

38. Danforth, C. H.: Relation of Genic and Endocrine Factors in Sex, in Allen, Danforth and Doisy,<sup>17</sup> chap. 6.

39. Courrier, R.: Nouvelles recherches sur la folliculine; contribution à l'étude du passage des hormones au travers du placenta, *Compt. rend. Acad. d. sc.* 179: 2192, 1924.

40. Greene, R. R.; Burrill, M. W., and Ivy, A. C.: Experimental Intersexuality: The Production of Feminized Male Rats by Antenatal Treatment with Estrogens, *Science* 88: 130 (Aug.) 1938; Experimental Intersexuality: The Paradoxical Effects of Estrogens on the Sexual Development of the Female Rat, *Anat. Rec.* 74: 429 (Aug.) 1939; Development of Intersexuality: The Effect of Antenatal Androgens on Experimental Intersexuality: The Effect of Antenatal Androgens on Sexual Development of Female Rats, *Am. J. Anat.* 65: 415 (Nov.) 1939. Hamilton, J. B., and Gardner, W. U.: Effects in Female Young Born of Pregnant Rats Injected with Androgens, *Proc. Soc. Exper. Biol. & Med.* 37: 570 (Dec.) 1937.

41. Newton, W. H.: Some Problems of Endocrine Function in Pregnancy, in Allen, Danforth and Doisy,<sup>17</sup> chap. 10.

42. Asdell, S. A.: Growth and Function of Corpus Luteum, *Physiol. Rev.* 8: 313 (July) 1928.

43. Pincus, Gregory: The Eggs of Mammals, New York, Macmillan Company, 1936.

44. Guthrie, Mary J., and Jeffers, Katharine R.: A Cytological Study of the Ovaries of the Bats *Myotis Lucifugus Lucifugus* and *Myotis Griseus*, *J. Morphol.* 62: 523, 1938.

45. Strong, L. C.; Gardner, W. U., and Hill, R. T.: Production of Estrogenic Hormone by a Transplantable Ovarian Carcinoma, *Endocrinology* 21: 268, 1937.

46. Parkes, A. S.: On the Occurrence of the Oestrous Cycle after X-Ray Sterilization: I. Irradiation of Mice at Three Weeks Old, *Proc. Roy. Soc., London, s. B.* 100: 172, 1926; IV. Irradiation of the Adult During Pregnancy and Lactation; and General Summary, *ibid.* 102: 51, 1927.

that follicles are normally the primary source of estrogen. They do prove that other tissues than follicles may undergo compensatory hypertrophy without follicular organization and retain this secretory function.

I think there is now evidence that all ovarian tissues may secrete estrogen—granulosa, theca, interstitial and luteal—but that follicular epithelium is probably normally the primary source. In the normal ovary the ova may be involved, for they are dynamic centers of the follicles. Primordial ova (without follicular appendages) may begin secretion of an "inductor." In birds the yolk contains estrogen.<sup>47</sup> The primary follicular fluid begins to form in partly developing follicles of mammalian ovaries, even after removal of the anterior lobe of the pituitary, as an intercellular secretion. The primary lakes of liquor folliculi first appear deep in the follicular epithelium. These follicles have very little theca, and the occurrence of interstitial cells is extremely variable in different species; therefore other possible sources do not exist at this time. Kingsbury<sup>48</sup> reported that interstitial cells are of variable and inconstant occurrence in ovaries of different species and are poorly developed before puberty even in the rabbit ovary, where later they are so conspicuous.

The changes in the follicle which precede ovulation, in fact, the changes which free the ovum from its attachment to the wall of the follicle and make its escape possible when the follicle ruptures, have been studied further in the rabbit by Pincus and Enzmann<sup>49</sup> and in the mouse by Snell and collaborators.<sup>50</sup> While the egg is still firmly attached by its cumulus to the follicle wall the nucleus is in resting condition.<sup>51</sup> When the ovum has become completely detached, the first maturation spindle has been completed and the first polar body formed. These phases of ovarian physiology would merit much more extensive discussion if limitations of space permitted.

The secretion of hormones by the ovaries is an ever expanding study. More than 40 estrogenic substances<sup>52</sup> have now been listed which act effectively in substituting for "the ovarian follicular hormone." Estradiol (dihydrotheelin) has been isolated from follicular contents and estrone (theelin) from sows' ovaries;<sup>53</sup> perhaps other estrogens are there. Freed and Soskin<sup>54</sup> postulated two estrogens with different properties from the ovaries of rats, one secreted by the granulosa and the other by the theca. Estrogens have been obtained from other than follicular sources: luteal tissue, ovaries without large follicles, and placental, chorionic and uterine tissues during pregnancy.<sup>52</sup>

Again there are several items of experimental evidence that show qualitative differences in the estrogenic content of tissues. For instance, luteal tissue from corpora of recent origin (corpora corresponding to eggs in the tubes) from human ovaries has a high

estrogenic content.<sup>55</sup> In several other mammals estrogen is absent from luteal tissue or present only in traces. In working with fresh tissue from human ovaries (immediately after operative removal), demonstration of estrogenic response from liquor folliculi and from walls of follicles which contained normal ova is relatively easy.<sup>56</sup> When degenerating eggs indicated that large follicles were atretic, negative results were frequent.

It is much more difficult to demonstrate progesterone than estrogen in human corpora lutea, as seen from the experiments of Pratt, Hamblen, Kamm and McGinty.<sup>57</sup> From excision of corpora at operation, however, there exists much evidence that is as good as actual recovery of this hormone.<sup>58</sup>

There is experimental evidence that in some mammals progesterone may be secreted by the follicle during the few hours before ovulation. Little is known about the modification in cell metabolism that must occur as the follicular cells, and perhaps to some extent those from the theca, transform to luteal cells.<sup>59</sup> There seems no obvious reason to object to a concept that postulates the secretion of follicular and later luteal hormones by the same cells at different phases of a life cycle of secretory activity.

The dividing line between follicle and corpus luteum was formerly placed at ovulation. This will not hold for accessory corpora as described earlier in this paper. The name "corpus luteum" is misleading, for only old corpora are truly "yellow bodies." Surely during the early stages of development from the large follicles a gradual transformation is indicated. Also, evidence is now accumulating to show that the large follicle may begin to change its secretion, perhaps toward the luteal type, before ovulation. The finding in mouse ovaries of a set of "intermediate follicular-luteal structures,"<sup>60</sup> in which part of the wall was luteal and part follicular (the part near the egg), has a bearing on this transformation. One line of evidence for this comes from the work of Young and collaborators.<sup>61</sup> They studied mating reactions (receptivity) of ovariectomized female guinea pigs treated by injection of estrogen and progesterone and showed that while a certain percentage would experience estrous behavior when given injections of estrogen alone, nearly all would react if first "primed" with estrogen and then given injections of progesterone. This secretion of progesterone by the preovulation follicle might be associated with the secretion of the watery secondary liquor folliculi. This secondary liquor is easily distinguishable by fixation and staining reactions from the primary liquor, which forms more gradually before late preovulation enlargement of the follicle begins.<sup>51</sup> But if the large follicle secretes progesterone, which had formerly been considered a specific secretion of the corpus luteum, one more of those artificial dividing lines between follicle

47. Allen, Edgar; Whitsett, J. W.; Hardy, J. W., and Kneibert, F. L.: The Follicular Hormone of the Hen Ovary, *Proc. Soc. Exper. Biol. & Med.* **21**: 500 (May) 1924.

48. Kingsbury, B. F.: Atresia and Interstitial Cells of the Ovary, *Am. J. Anat.* **65**: 309 (Sept.) 1939.

49. Pincus, Gregory, and Enzmann, E. V.: The Growth, Maturation and Atresia of the Ovarian Eggs of the Rabbit, *J. Morphol.* **61**: 351, 1937.

50. Snell, G. D.; Fekete, Elizabeth; Hummel, Katharine P., and Law, L. W.: The Relation of Mating, Ovulation and the Estrous Smear in the House Mouse to Time of Day, *Anat. Rec.* **76**: 39 (Jan.) 1940.

51. Robinson, A.: The Formation, Rupture, and Closure of Ovarian Follicles in Ferrets and Ferret-Polecat Hybrids, and Some Associated Phenomena, *Tr. Roy. Soc. Edinburgh* **52**: 302, 1918.

52. Doisy, E. A.: Biochemistry of Estrogenic Compounds, in Allen, Danforth and Doisy, chap. 13.

53. Westerfeld, W. W.; Thayer, S. A.; MacCorquodale, D. W., and Doisy, E. A.: The Ketonic Estrogen of Sow Ovaries, *J. Biol. Chem.* **126**: 181 (Nov.) 1938.

54. Freed, S. C., and Soskin, Samuel: Complete and Incomplete Estrogenic Hormones Arising from Different Sites in the Rat's Ovary, *Endocrinology* **21**: 599 (Sept.) 1937.

55. Allen, Edgar; Pratt, J. P.; Newell, O. U., and Bland, L. J.: Hormone Content of Human Ovarian Tissues, *Am. J. Physiol.* **92**: 127 (Feb.) 1930.

56. Allen, Edgar: Human Ova from Large Follicles: Including a Search for Maturation Divisions and Observations on Atresia, *Am. J. Anat.* **46**: 1 (July) 1930.

57. Pratt, J. P.; Hamblen, E. C.; Kamm, O., and McGinty, D. A.: The Human Corpus Luteum and Progesterone, *Endocrinology* **20**: 741 (Nov.) 1936.

58. Allen, Edgar; Hisaw, F. L., and Gardner, W. U., in Allen, Danforth and Doisy, chap. 8.

59. Hartman, C. G.: Studies on Reproduction in the Monkey and Their Bearing on Gynecology and Anthropology, *Endocrinology* **25**: 670 (Nov.) 1939.

60. Allen, Edgar; Smith, G. M., and Gardner, W. U.: Growth of Ovaries and Genital Tract in Response to Hormones as Studied by the Colchicine Technique, *Anat. Rec.* **67** (supp. 3): 3, (March) 1937.

61. Young, W. C.; Dempsey, E. W.; Myers, H. I., and Hagquist, C. W.: The Ovarian Condition and Sexual Behavior in the Female Guinea Pig, *Am. J. Anat.* **63**: 457 (Nov.) 1938.

and corpus luteum used for the convenience of definition becomes less distinct.

The question of secretion of specific hormones by certain recognized tissues needs further discussion. Before the study of the distribution of estrogen in ovarian tissues was completed, the substance was isolated from the placenta,<sup>62</sup> and ovariectomy during early pregnancy<sup>63</sup> showed that the placenta elaborated, rather than stored, estrogen. Further evidence for the secretion of estrogens by the placenta comes from the continuation of estrogenic effects of placental origin when the embryos are killed while the placentas are retained; i. e. (1) the continued growth of the mammary glands, (2) the continued support of luteal function and (3) the continued regulation of water balance (retention) typical of pregnancy.<sup>41</sup>

One of the most outstanding features in ovarian physiology continues to be the remarkable domination of late follicular development and ovulation by the anterior lobe of the pituitary.<sup>64</sup> Apparently follicles can develop to fairly large size—to almost the full size of the ovum with several layers of follicle cells and the formation of small amounts of follicular fluid—without need for anterior pituitary stimulation. This is true in the rat after complete removal of the anterior lobe of the pituitary. However, further follicular development and ovulation and also the formation of corpus luteum require anterior pituitary stimulation.<sup>65</sup> If additional follicle-stimulating hormone is present, many more follicles develop than normally. This shows that limitation of this particular hormone is a normal condition.

Many measurements of ovarian ova of mammals have shown that before much fluid is secreted and accumulated in the follicle as liquor folliculi, the egg has reached its full size. Since this stage of follicular development is reached in hypophysectomized animals, the growth of the egg and early growth of the follicle are independent of anterior pituitary hormones. Pituitary stimulation undoubtedly plays a primary part in stimulating later secretion of liquor folliculi. It also may be involved in the maturation of the ovum just before ovulation and in ovulation itself; Pincus thinks that this effect is on the follicle cells rather than on the ovum, because the initiation of the first maturation division occurs in vitro simply on explantation of ovarian eggs from the follicles.<sup>48</sup>

Conditions at puberty which initiate cyclic sexual activity are extremely important. This undoubtedly involves interaction between the ovaries and the pituitary. It is probable that at the approach of adolescence estrogen from partly developing follicles influences the anterior lobe of the pituitary, at first stimulating, then depressing pituitary secretion of the follicle-stimulating hormone. Clark<sup>66</sup> reported the content of this hormone to be higher in the female than in the male rat at puberty, although later the male pituitary is more potent than that of the female. Frank<sup>67</sup> reported that low doses of estrogen stimulate,

while high doses depress, pituitary gonadotropic function. The atresia of the majority of the group of large follicles would permit the increased secretion of the pituitary which is so vital for the late development of large follicles of the next generation. A succession of several partial (anovulatory) estrous or menstrual cycles which result from these ovarian pituitary relationships is the usual condition at adolescence of certain primates.<sup>68</sup> Puberty is usually not a sudden event but a gradual transition.<sup>69</sup> These conditions can be duplicated by injection experiments with estrogens. Several repetitions of a dose of estrogen subthreshold for an initial menstruation in the infantile monkey finally produce the first menstrual period.<sup>68</sup> Since effects of injected estrogens on the uterus itself appear to be transitory, the explanation probably must include interaction between ovarian estrogen and anterior pituitary gonadotropin.

Cystic follicles in the ovary have long worried the gynecologist. They are now easily produced experimentally by excessive or unbalanced stimulation with anterior pituitary gonadotropic extracts. In early stages of this condition a hyperestrogenic effect on the genital tract and mammary glands is usually present. Cystic follicles occur spontaneously in one genetic strain of rats,<sup>69</sup> which consequently remain for long periods in estrus (constant estrus rats), and Everett<sup>70</sup> has succeeded, by injections of progesterone, in inducing ovulation of these follicles.

Pfeiffer<sup>71</sup> has produced this condition of constant estrus by experimental modification of anterior pituitary gonadotropic function. One of the remarkable things about this experiment is that the effect is more than transitory; i. e., most endocrine effects disappear quickly after treatment with tropic substances is stopped, but in Pfeiffer's experiment altered anterior pituitary function continues after removal of the modifying factor. He transplanted testes from litter mates into 1 day old female mice. Since this was done in a closely inbred strain of mice, the grafted testes were vascularized and matured normally. The ovaries matured normally, and also the female accessory genital organs, but the animals were subject to "constant estrus," instead of "cyclic estrus," and did not recover from this condition even after the grafted testes were removed. Pfeiffer has explained these results as experimental modification by the testis grafts of the level or of the quality of anterior pituitary gonadotropic secretion. In rats similarly treated the injection of a pituitary extract containing the luteinizing principle induces ovulation; the animals mate and may become pregnant.<sup>72</sup> They often have difficulty in carrying pregnancy to term, but additional injections of the same extract make normal gestation and parturition possible.

The surgeon, confronted at laparotomy by cystic ovaries after symptoms of long duration, may think ovariectomy necessary, as it probably is in extreme cases. Experimental modification of anterior pituitary function, however, might remove the actual cause. Experiments of van Wageningen and Morse<sup>73</sup> point in this

62. Allen, Edgar; Pratt, J. P., and Doisy, E. A.: The Ovarian Follicular Hormone, *J. A. M. A.* **85**: 399 (Aug. 8) 1925.

63. Waldstein, E.: Frühkastration in der Schwangerschaft, *Zentralbl. f. Gynäk.* **53**: 1305 (May 25) 1929.

64. Zondek, Bernhard, and Aschheim, S.: Hypophysenvorderlappen und Ovarium. Beziehungen der endokrinen Drüsen zur Ovarialfunktion, *Arch. f. Gynäk.* **130**: 1, 1927. Smith and Engle.<sup>70</sup>

65. Smith, P. E., and White, W. E.: The Effect of Hypophysectomy on Ovulation and Corpus Luteum Formation in the Rabbit, *J. A. M. A.* **97**: 1861 (Dec. 19) 1931.

66. Clark, H. M.: A Prepubertal Reversal of the Sex Difference in the Gonadotropic Hormone Content of the Pituitary Gland of the Rat, *Anat. Rec.* **61**: 175, 1935; A Sex Difference in the Change in Potency of the Anterior Hypophysis Following Bilateral Castration in Newborn Rats, *ibid.* **61**: 193 (Jan.) 1935.

67. Frank, R. T.: The Sex Hormones; Their Physiologic Significance and Use in Practice, *J. A. M. A.* **114**: 1504 (April 20) 1940.

68. Allen, Edgar; Diddle, A. W.; Burford, T. H., and Gardner, W. U.: Ovarian Hormone Threshold for Experimental Menstruation in Monkeys, *Am. J. Physiol.* **117**: 381 (Nov.) 1936.

69. Everett, J. W.: Spontaneous Persistent Estrus in a Strain of Albino Rats, *Endocrinology* **25**: 123 (July) 1939.

70. Everett, J. W.: The Restoration of Cyclic Estrus and Ovulation in Persistent-Estrous Rats by Progesterone, *Anat. Rec.* **76** (supp. 2): 21 (Feb.) 1940.

71. Pfeiffer, C. A.: The Effects of an Experimentally Induced Endocrine Imbalance in Female Mice, *Anat. Rec.* **75**: 465, (Dec.) 1939.

72. Pfeiffer, C. A.: Maintenance of Pregnancy in Constant-Estrous Female Rats, *Anat. Rec.* **76** (supp. 2): 45 (Feb.) 1940.

73. Van Wageningen, Gertrude, and Morse, A. H.: Pregnancy Following Induced Cystic Changes in the Ovaries, *Lancet* **1**: 1220 (May 28) 1938.

direction. By long-continued injections of an anterior pituitary extract containing the gonadotropic principles they succeeded in producing in monkeys extremely cystic ovaries, demonstrated by laparotomy. Treatment was then withdrawn. Recovery of normal ovarian function was shown when animals later mated, carried normal pregnancies to birth at term and nursed their offspring.

Another instance of the dependence of ovarian function on anterior pituitary hormone is the trigger mechanism of ovulation in the rabbit (also in the cat and ferret). Stimulation of the cervix uteri affects the pituitary, apparently through a nerve pathway; pituitary secretion within the next few hours induces ovulation about ten hours later. The time cited was proved by removal of the anterior lobe of the pituitary, which, if left intact for one hour after mating, functioned sufficiently to induce ovulation.<sup>74</sup> Then cytologic evidence for this transient pituitary function was discovered by Friedgood and Dawson<sup>75</sup> in the existence of cells which react to special stains only during the few hours when this transient function exists.

Much work has been done in the last ten years on the physiology of ovulation itself. This began with the actual observation of ovulation by Walton and Hammond<sup>76</sup> in 1929. The process has since been photographed in several animals. While in the of muscles in the wall of the follicle undoubtedly is of major force in ovulation,<sup>77</sup> in mammals increase in intrafollicular pressure is probably the dominant force. This is due to increase in secretion of the liquor folliculi, which forms rapidly in the pre-ovulation follicle, and there is good evidence that this secretion is in response to pituitary stimulation. Events which directly precede ovulation include extreme stretching and "blowing out a pimple" in the weakest point of the follicle wall, a compression of the capillary net at this point, which leaves an avascular stigma, which finally breaks and through which follicular contents are extruded.<sup>78</sup> Before actual rupture of the follicle there may be a leakage of the more fluid follicular contents at this point, and then a rather sudden rupture and extrusion of the more viscous follicular contents, including the ovum with its cumulus of follicle cells still surrounding it.<sup>78</sup>

In some animals, notably the rabbit, the rupture of the follicle is accompanied by a remarkable change in electrical potential<sup>79</sup> as measured between the cervix and the symphysis pubis. In some other animals, which bear large litters, there may be a continued rise in electrical potential before ovulation with marked fluctuations in potential at the time the eggs are being ovulated,<sup>80</sup> but it may not be possible to associate a single rise in potential with the rupture of a specific follicle.<sup>81</sup>

Studies of changes in electrical potential have been made during the menstrual cycle in women.<sup>82</sup> In some instances the changes have been correlated with ovulation. At present it appears that alterations in potential, although occurring most frequently between successive periods, occur also at other times in the cycles in some women.<sup>83</sup> This indicates ovulation at other than the recognized usual time of ovulation in the cycle, or else the possibility that advanced development of follicles without ovulation may influence the rise in potentials.

Studies of the ovum and the follicles just preceding ovulation, especially those by Robinson and by Pincus, have greatly advanced the knowledge of the physiology of the ovary at this time. Reference is made to Pincus's book<sup>43</sup> for discussion of these stages.

During various phases of egg production, atresia, corpus luteum formation and retrogression, interstitial tissue appears. This is more abundant in some mammalian ovaries than in others; in some normal ovaries interstitial tissue may be very poorly developed or absent.<sup>48</sup> In broad definition interstitial tissue may include epithelioid cells between follicles or corpora, connective and vascular tissues being excluded. One source of formation of interstitial tissue is the proliferation of cells about a growing follicle to form the theca interna. This proliferation is readily gaged in normal ovaries by means of the drug colchicine, which shows proliferating follicles to have almost as many mitoses in the surrounding theca as among the granulosa cells of the follicles. Theca cells of growing follicles are really part of the follicle rather than "interstitial," but they become interstitial when atretic follicles undergo degeneration; in fact, Kingsbury stressed the principal derivation of interstitial cells in the ovary of the cat from thecal remains. As the follicle degenerates, the lipid content of these cells increases. In this phase of its activity the theca of atretic follicles should not be confused with the theca of rapidly growing follicles as described by Mossman in the pocket gopher. Other interstitial cells may be derived by invaginations from the germinal epithelium, certain nests of cells or "anovular follicles," or possibly by cell multiplication in situ. The term "interstitial cells" as proposed by Bouin carries the inference of secretion. Accumulation of lipids in these cells has been interpreted by Kingsbury<sup>48</sup> as storage rather than secretion.

There is now a considerable accumulation of experimental evidence that pituitary secretion is necessary for the proper formation and function of corpora lutea. Although the pituitary seems in these ways to dominate the ovaries, there is adequate evidence to show that the secretions of the ovaries react forcibly on the pituitary. The effects of ovariectomy in inducing castration changes in the pituitary, the prevention of these changes by injected estrogens,<sup>84</sup> the tumors of the pituitary following excessive estrogenic stimulation,<sup>85</sup> all point to the importance of the influence of ovarian secretions on the pituitary.

74. (a) Fee, A. R., and Parkes, A. S.: Studies on Ovulation: I. The Relation of the Anterior Pituitary to Ovulation in the Rabbit, *J. Physiol.* **67**:383 (July) 1929. (b) Deanesly, R.; Fee, A. R., and Parkes, A. S.: Studies on Ovulation: II. Effect of Hypophysectomy on Formation of the Corpus Luteum, *J. Physiol.* **70**:38 (Aug.) 1930.

75. Friedgood, H. R., and Dawson, A. B.: Cytologic Evidence of the Gonadotropic Activity of the Rabbit's Anterior Hypophysis, *Endocrinology* **22**:674 (June) 1938.

76. Walton, A., and Hammond, J.: Observations on Ovulation in the Rabbit, *Brit. J. Exper. Biol.* **6**:190, 1928.

77. Kuch, R.: Ovulation in the Frog: II. Follicular Rupture to Fertilization, *J. Exper. Zool.* **71**:163 (July) 1935.

78. Hill, R. T.; Allen, Edgar, and Kramer, T. C.: Cinemicrographic Studies of Rabbit Ovulation, *Anat. Rec.* **63**:239 (Oct.) 1935.

79. Burr, H. S.; Hill, R. T., and Allen, Edgar.: Detection of Ovulation in the Intact Rabbit, *Proc. Soc. Exper. Biol. & Med.* **33**:109 (Oct.) 1935.

80. Rogers, P. V.: Electric Potentials in Normal Castrate, and Theelin Treated Rats, *Proc. Soc. Exper. Biol. & Med.* **35**:257 (June) 1936.

81. Rohrer, J. L.; Barton, Dorothy S., and Burr, H. S.: Vaginal Electrical Correlates of the Estrous Cycle of the Rat, *Anat. Rec.* **76** (Supp. 2):18 (Feb.) 1939.

82. Burr, H. S., and Musselman, L. K.: Bio-Electric Phenomena Associated with Menstruation, *Yale J. Biol. & Med.* **9**:155 (Oct.) 1936. Rock, John; Reboul, Jean, and Wiggers, H. C.: The Detection and Measurement of the Electrical Concomitant of Human Ovulation by Use of the Vacuum-Tube Potentiometer, *New England J. Med.* **217**:634 (Oct. 21) 1937.

83. Burr, H. S.; Musselman, L. K.; Barton, Dorothy S., and Kelly, Naomi B.: Bio-Electric Correlates of Human Ovulation, *Yale J. Biol. & Med.* **10**:155 (Dec.) 1937.

84. Fevold, H. L.: Follicle Stimulating and Luteinizing Hormones of Anterior Pituitary in Allen, Danforth and Doisy,<sup>11</sup> chap. 17.

85. Cramer, W., and Horning, E. S.: Experimental Production by Oestrin of Pituitary Tumors with Hypopituitarism and of Mammary Cancer, *Lancet* **1**:247 (Feb. 1) 1936. McEuen, C. S.; Selye, Hans, and Collip, J. B.: Some Effects of Prolonged Administration of Oestrin in Rats, *ibid.* **1**:775 (April 4) 1936.

Ovarian function during pregnancy was first studied because of the importance of the corpus luteum to continued gestation. It has been known for a long time that the growth of follicles is inhibited during pregnancy (and also during lactation). With the recognition of the placenta (and of the chorion in case no true placenta is formed) as a source of estrogen in the pregnant animal, its function compensatory to the ovaries was indicated. First it was shown that removal of the anterior lobe of the pituitary after mating prevented the formation and function of the corpora lutea.<sup>74a</sup> Then injections of estrogen in hypophysectomized animals were known to prevent involution of the corpora. Recently Greep<sup>14</sup> has shown that if the pregnant uterus is removed from the rabbit on the tenth or fifteenth day of gestation, the corpora involute, and new follicles begin growth. If estrogen is injected into such animals, this involution of the corpora is prevented. However, Greep could not demonstrate estrogen in the rabbit placenta.

Snyder's<sup>86</sup> successful demonstration of stimulation of ovulation late in pregnancy, followed by superfetation, shows that follicular development is inhibited by deficiency of anterior pituitary hormone. He did this by injections of pregnancy urine in the rabbit late in gestation. This was one of the first experimental demonstrations of superfetation. This procedure usually prevented parturition.

A discussion of ovarian function would not be complete without citation of the evidence for secretion of androgen by the ovaries under certain conditions. It has been well established that androgens are excreted by females,<sup>25</sup> and at first the source was attributed to the adrenals, because of the masculinizing effects of tumors of the adrenal cortex. Hill<sup>85</sup> demonstrated clearly that ovarian tissue can, under certain conditions, secrete androgen. Using closely inbred strains of mice, he grafted ovaries in the ears of males. After the grafted ovaries had become vascularized, the testes were removed. In some cases, especially during a hot summer, the seminal vesicles and the prostate would undergo castrate atrophy; in others, especially during the winter, the accessory male organs were maintained in good functional condition. Hill<sup>87</sup> was then able to demonstrate an effect of temperature (the ovaries being implanted in the thin ears of the mouse were quickly subjected to environmental temperatures). When castrated males with ovaries grafted in their ears were living in warm temperatures, the seminal vesicles and prostates atrophied. When the same animals were removed to cool quarters, these accessory organs were maintained in functional condition, as shown by both organ weights and the appearance of intracellular secretory granules. After such proof one must consider the possibility of factors other than temperature modifying ovarian secretion from the estrogenic to the androgenic type—in fairly normal ovarian tissue as well as in the clearly pathologic arrhenoblastoma. Mere hypertrophy in the absence of a clearly demonstrable tumor might well be sufficient to account for varying degrees of masculinization in young girls.

Studies of changes in bones of birds<sup>88</sup> show formation of new spicules of cancellous bone in the marrow

cavities at the time when eggs are ripening in the ovaries—and extreme conditions of a similar nature induced experimentally in both birds<sup>89</sup> and mammals (mice)<sup>90</sup> by injections of estrogens emphasize the importance of estrogenic ovarian hormone on calcium metabolism and bone structure. That a similar mechanism may be involved in the normal pneumatization of bones in birds is indicated in recent studies of the chick by Bremer,<sup>91</sup> who emphasized the similarity of the osseous changes preceding this invasion of the bones by the air sacs to the pathologic condition osteitis fibrosa.

At the same time at which new bone is replacing marrow in the long bones and even in the axial skeleton of the mouse under estrogenic stimulation, bone is being resorbed from the symphysis pubis,<sup>90</sup> as occurs in normal mice toward the end of pregnancy.

The profound effect of the seasonal variation in the length of daylight on ovarian function of some birds and a few seasonally breeding mammals has been established.<sup>92</sup> Increased egg laying in fowls through the winter from increased lighting is a commonplace in modern farming. Benoit's<sup>93</sup> work in the duck, which conclusively demonstrated the influence of a light stimulus through the eyes to the anterior lobe of the pituitary and thence on the gonads, furnishes concrete experimental evidence. The work of Kirschbaum and Pfeiffer<sup>94</sup> in sparrows, in which a differential response of ovaries and transplanted testes to light was demonstrated, carries the solution further. Recently it has been shown that the timing of ovarian function—follicular maturation and ovulation—can be reversed in nocturnal animals, e. g., the rat<sup>95</sup> and the mouse,<sup>96</sup> by reversing day and night light conditions.

The physiology of the ovary at and after the time of the menopause is an extremely interesting subject which can only be touched on in the present chapter. One thing which is certain is that ovulation usually stops at the menopause. This eliminates consideration of the endocrine function of newly forming corpora lutea after this time. The secretion of old corpora might persist for several months in diminishing amounts. However, even after the menopause follicles develop partly for several years. Follicles may also become cystic at this time. But as a generalization it might be said that usually internal secretion of the postmenopausal ovary is definitely declining. Concurrently there is an increase in the amount of the gonadotropic substance which appears in the urine.<sup>96</sup> The same is true of the premature menopause following ovariectomy.<sup>97</sup>

89. Landauer, W.; Pfeiffer, C. A.; Gardner, W. U., and Man, E. B.: Hypercalcemia, -Calcemia and -Lipemia in Chickens Following Administration of Estrogens, *Proc. Soc. Exper. Biol. & Med.* **42**: 89 (May) 1939.

90. Gardner, W. U., and Pfeiffer, C. A.: Skeletal Changes in Mice Receiving Estrogens, *Proc. Soc. Exper. Biol. & Med.* **37**: 678 (Jan.) 1938.

91. Bremer, J. L.: The Pneumatization of the Bones of the Chick and the Association Activity of Theelin, *Anat. Rec.* **76** (suppl. 2): 9 (Feb.) 1940.

92. Bissonnette, T. H.: The Influence of Light upon Pituitary Activity, *Proc. A. Research in Nerv. & Ment. Dis.*, *Proc.* (1936) **17**: 361, 1938.

93. Benoit, Jacques: Stimulation of the Hypophysis and Genital Glands in the Duck by Electric Light: Effect of Thyroidectomy on the Testis and Liver, *Anat. Rec.* **67** (suppl. 1): 81, 1936.

94. Kirschbaum, A.; Pfeiffer, C. A.; Van Heuversseyn, J. D., and Gardner, W. U.: Studies on Gonad-Hypophyseal Relationship and Cyclic Osseous Changes in the English Sparrow, *Passer Domesticus* L., *Anat. Rec.* **75**: 249 (Oct.) 1939.

95. Hemmingsen, A. M., and Krarup, N. B.: Rhythmic Diurnal Variations in the Oestrous Phenomena of the Rat and Their Susceptibility to Light and Dark, Copenhagen, Levin & Munksgaard.

96. Fluhmann, C. F.: The Endometrium in So-Called Idiopathic Uterine Hemorrhage, *J. A. M. A.* **93**: 1136 (Oct. 12) 1929.

97. Fluhmann, C. F.: The Blood of the Anterior Pituitary Gland in the Blood of Women: A Preliminary Causal Study in Non-Pregnant Individuals, *Endocrinology*, **20**: 1, (July) 1930; *Anterior Pituitary Gland in the Blood of Women: A Preliminary Causal Study in Non-Pregnant Individuals*, *Endocrinology*, **20**: 1, (July) 1930.

86. Snyder, F. F.: The Prolongation of Pregnancy and Complications of Parturition in the Rabbit Following Induction of Ovulation near Term, *Bull. Johns Hopkins Hosp.* **54**: 1 (Jan.) 1934.

87. Hill, R. T.: Ovaries Secrete Male Hormone: III. Temperature Control of Male Hormone Output by Grafted Ovaries, *Endocrinology* **21**: 635 (Sept.) 1937.

88. Kyes, P., and Potter, T. S.: Physiological Marrow Ossification in Female Pigeons, *Anat. Rec.* **60**: 377 (Nov.) 1934.



One point of extreme importance in the endocrine function of the postmenopausal ovary is the possibility of a shift toward secretion of androgen at this time. Masculinization phenomena and hypertrichosis occurring in a few women after the menopause require the inclusion of consideration of this possibility.

Ten years after the menopause the ovary is represented by a mere fibrous fold of tissue, very small and obviously not very important from the point of view of production of either eggs or hormones. Apparently ovarian function declines while the gonadotropic function of the pituitary is still efficient.

## Council on Foods and Nutrition

THE COUNCIL HAS AUTHORIZED PUBLICATION OF THE FOLLOWING REPORT.  
FRANKLIN C. BING, Secretary.

### VITAMIN D MILK CONTAINING 600 U. S. P. UNITS OF VITAMIN D TO THE QUART IS NOT ELIGIBLE FOR LIST OF ACCEPTED FOODS

When vitamin D milk first was made commercially available, there were two general methods for its production. The irradiation method was capable of producing a milk containing at least 135 U. S. P. units of vitamin D to the quart. Recently there have been developed suitable methods of irradiating milk so that the resulting product contains at least 400 U. S. P. units of vitamin D to the quart. The vitamin D milk produced by the method of adding a vitamin D preparation, such as cod liver oil concentrate, has contained at least 400 U. S. P. units of vitamin D to the quart. The selection of this level of fortification at first was more or less fortuitous. At the time, now more than ten years ago, it was erroneously believed that one quart of such milk was equivalent to the vitamin D value of 3 teaspoons of cod liver oil, the then recommended daily dosage for infants. Subsequently it was learned that cod liver oil had a higher potency, and at present U. S. P. cod liver oil contains at least 85 units to the gram, or approximately 310 units to a theoretic teaspoon of 4 cc. This means that one quart of vitamin D milk containing 400 U. S. P. units of vitamin D is equivalent in vitamin D potency to one and one-third teaspoon of minimum strength U. S. P. cod liver oil to the quart. Even before the commercial production of these milks containing either 135 or 400 units of vitamin D to the quart, scientific and clinical evidence was obtained to show their nutritive value. A number of reviews of reports of these and subsequent studies have been published.<sup>1</sup> A paper by Jeans and Stearns<sup>2</sup> affords a discussion of recent available evidence on factors affecting vitamin D requirements. For the prevention of rickets, for good bone and tooth development and for excellent growth it appears that the vitamin D requirements of the full term artificially fed baby are satisfied if each quart of milk consumed contains between 300 and 400 U. S. P. units of vitamin D. Babies receiving human milk may require less vitamin D than babies receiving cow's milk. For children between infancy and adolescence, a daily allowance of 750 to 1,000 cc. (about 1½ to 2 pints) of milk containing from 300 to 400 U. S. P. units of vitamin D permits ample retention of calcium and phosphorus. For adolescents, data are not sufficiently numerous to permit an estimate of the quantity required, but there seems to be no reason why it should be less than the

requirement of the baby. The requirements of adults for vitamin D are not known; during pregnancy and lactation the requirement is increased. A daily dosage of 800 units or more has been suggested for the lactating woman, together with an abundant intake of calcium and phosphorus.<sup>3</sup>

There now has been presented to the Council for consideration with a view to acceptance milk which has been fortified with 600 U. S. P. units of vitamin D to the quart. Except in the cases of some lactating women, evidence is meager that milk containing more than 400 U. S. P. units of vitamin D to the quart would have any nutritional advantages over milk containing but 400 U. S. P. units to the quart. For persons who need more than the amount of vitamin D which can be provided with suitable amounts of vitamin D milk containing 400 U. S. P. units of vitamin D to the quart, numerous other preparations can be prescribed, such as those described in New and Nonofficial Remedies.<sup>3</sup> Incidentally, it may be stated further that the Council believes preparations such as those described in N. N. R. are fully as effective, unit for unit, as vitamin D in the form of vitamin D milk, provided the concentration of vitamin D is not appreciably greater than 180 units to a gram of oil.

For the foregoing reasons, the Council has voted not to include for the present in the list of accepted foods any brands of milk for which claims are made that they contain more than 400 U. S. P. units of vitamin D to the quart. The evidence hitherto available suggesting the desirability of a higher amount of vitamin D in milk for protection from dental caries is not considered conclusive. Should evidence be developed to indicate that milk of higher potency is nutritionally desirable, the Council then will give further consideration to the acceptability of such products.

## ACCEPTED FOODS

THE FOLLOWING ADDITIONAL FOODS HAVE BEEN ACCEPTED AS CONFORMING TO THE RULES OF THE COUNCIL ON FOODS OF THE AMERICAN MEDICAL ASSOCIATION FOR ADMISSION TO ACCEPTED FOODS.

FRANKLIN C. BING, Secretary.

### PREPARATIONS USED IN THE FEEDING OF INFANTS (See Accepted Foods, p. 156).

H. J. Heinz Company, Pittsburgh.

HEINZ BRAND CHOPPED CARROTS.

*Analysis* (submitted by manufacturer).—Moisture 93.1%, total solids 6.9%, ash 0.8%, fat (ether extract) 0.1%, protein (N  $\times$  6.25) 0.9%, crude fiber 0.7%, carbohydrates other than crude fiber (by difference) 4.4%, sucrose (Munson and Walker Method) 3.9%, calcium (Ca) 0.038%, phosphorus (P) 0.021%, iron (Fe) 0.0015%, copper (Cu) 0.00004%.

According to a report of biologic assay (1939) this product contains 4,000 international units of vitamin A, 12 international units of vitamin B<sub>1</sub> and 23 Sherman-Bourquin units of riboflavin per hundred grams. Report of chemical titration (1939) shows that the product contains 62 international units of vitamin C per hundred grams.

*Calories*.—0.22 per gram; 6 per ounce.

HEINZ BRAND CREAMED DICED VEGETABLES WITH CEREALS AND YEAST CONCENTRATE, a canned cooked mixture of milk, celery, carrots, white potatoes, tomatoes, onions, rice, sodium chloride, sugar, flour, and autolyzed yeast concentrate.

*Analysis* (submitted by manufacturer).—Moisture 86.1%, total solids 13.9%, ash 1.5%, fat (ether extract) 1.2%, protein (N  $\times$  6.25) 2.1%, crude fiber 0.3%, carbohydrates other than crude fiber (by difference) 8.8%, sucrose (Munson and Walker method) 2.5%, calcium (Ca) 0.099%, phosphorus (P) 0.061%, iron (Fe) 0.0012%, copper (Cu) 0.00011%.

According to report of biologic assay (1939) this product contains 1,150 international units of vitamin A, 7 international units of vitamin B<sub>1</sub> and 54 Sherman-Bourquin units of riboflavin per hundred grams. Report of chemical titration (1939) shows that the product contains 62 international units of vitamin C per hundred grams.

*Calories*.—0.54 per gram; 15 per ounce.

### SUGARS AND SYRUPS (See Accepted Foods, 1939, p. 324).

Bliss Syrup & Preserving Co., Kansas City, Mo.

BLISS BRAND WAFFLE SYRUP, a mixture of corn syrup and cane sugar syrup, flavored with imitation maple flavoring.

*Analysis* (submitted by manufacturer).—Moisture 24%, total solids 76%, ash 0.3%, protein (N  $\times$  6.25) 0.7%, reducing sugars as dextrose before inversion 28.7%, total carbohydrate (by difference) 75%.

*Calories*.—3.0 per gram; 85 per ounce.

NECTAR BRAND WAFFLE SYRUP, same as Bliss Brand Waffle Syrup.

3. New and Nonofficial Remedies, Chicago, American Medical Association, 1940, p. 532.

1. Jeans, P. C.: Vitamin D Milk. *J. A. M. A.* **106**:2066 (June 13), 2150 (June 20) 1936. Report of the Council on Foods: The Present Status of Vitamin D Milk, *ibid.* **108**:206 (Jan. 16) 1937. Report of the Council on Foods: Vitamin D Milk Produced by Feeding Cows Irradiated Yeast, *ibid.* **109**:1814 (Nov. 27) 1937.

2. Jeans, P. C., and Stearns, Genevieve: The Human Requirement of Vitamin D. *J. A. M. A.* **111**:703 (Aug. 20) 1938; in *The Vitamins*, A Symposium, Chicago, American Medical Association, 1939, chapter 26, p. 483.

# THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

535 NORTH DEARBORN STREET - - - CHICAGO, ILL.

Cable Address - - - "Medic, Chicago"

Subscription price - - - : Eight dollars per annum in advance

Please send in promptly notice of change of address, giving both old and new; always state whether the change is temporary or permanent. Such notice should mention all journals received from this office. Important information regarding contributions will be found on second advertising page following reading matter.

SATURDAY, FEBRUARY 1, 1941

## HYGIENE IN AIR RAID SHELTERS

As a result of the vast numbers seeking the relative safety of air raid shelters in the London metropolitan area, many difficult and unexpected health and sanitary problems have arisen. At a meeting on this subject of the Section on Epidemiology and State Medicine at the Royal Society on Dec. 20, 1940, reported in the *British Medical Journal*,<sup>1</sup> many of the pressing questions on this subject were discussed, including ventilation, heating, the establishment of medical aid posts in the larger shelters, measures against lice-borne disease, the provision of sanitary facilities, masking for the prevention of droplet infection, the use of insecticides, the disinfection of air and the problems of overcrowding. Two compensating factors were pointed out by Lord Horder: the stimulation of research which would undoubtedly lead to invaluable and permanent contributions to preventive medicine, and the opening up of a field for health education quite unparalleled in the past.

In the same issue of the *British Medical Journal* appear the further proposals of Lord Horder's Committee on Health in Air Raid Shelters<sup>2</sup> as presented to parliament by the Ministry of Health and the Ministry of Home Security. The committee recommended that arrangements be made to hospitalize those persons with "open" tuberculosis known to frequent shelters and further that each tuberculous family should have a family shelter. Compulsory powers to enforce these regulations are apparently already in effect.

The louse and other pests have necessitated serious thought. A short course of instruction for shelter wardens and a pamphlet giving briefly the life history of the louse, flea and bedbug and outlining simple measures for dealing with these pests are methods

which have been evolved. Insecticides have been chosen and made available or have been ordered and further research has been begun. Compulsory powers have been established to delouse when necessary. The committee urged that the construction of shelter bunks and other fittings avoid as far as possible cracks, crevices and other harborages for insects. When shelters are found infested the committee suggested the adoption of a method of cleaning and scrubbing with soap and water containing cresol, together with the use of a painter's blow lamp to cracks and the like.

In the consideration of droplet infections and the preventive value of face masks, the committee recommended a cellulose acetate (cellophane) screen as the best for standard purposes. These have been ordered in quantity, but the committee did not object to certain other masks including the gauze type. From the evidence placed before it, the committee concluded that there were not sufficient grounds on which to recommend any of the reputed prophylactic measures such as medicated lozenges, gargles and throat sprays for use against infection in the shelters. It did not, however, advise against any of these measures for individual users of shelters. Smoking in public shelters should be avoided except when a separate compartment can be set aside. Finally, the committee is sponsoring certain controlled experiments with some of the newer forms of chemotherapeutic drugs used as nose and throat sprays under medical supervision.

At the discussion on December 20, Dr. P. G. Stock of the Ministry of Health stated that the shelter peak population of the underground tubes (subways) was reached in September at 186,000 but that it had fallen to about 100,000 at the time of the discussion. The hygienic problem in the tubes, however, constitutes only one aspect of the health problem in the shelters.

## THE CHIROPRACTIC THEORY OF LAW

Chiropractic is a distorted technic for the diagnosis and treatment of disease, which is being foisted on the American people, notwithstanding that its advocates lack the slightest conception, let alone appreciation, of the most elementary and clearly demonstrable facts in connection with the human body in health and disease. The realities of anatomy, pathology, physiology and chemistry mean nothing to chiropractors. Nevertheless, any informed person who points out the inanity of their theories and the baneful effects of their treatment is, by their propaganda, bigoted, hidebound, reactionary.

Chiropractors are in general quite uninformed in the field in which they hold themselves out as having some knowledge or aptitude. When they digress into other fields, they usually reveal such appalling ignorance that even the most casual observers see them in their true light. Few people realize that chiropractors, unlike

1. Hygiene in Air Raid Shelters, a discussion on Hygiene in Air Raid Shelters, Dr. J. Allison Glover presiding. Reports of Societies, Brit. M. J. 1: 26 (Jan. 4) 1941.

2. Health in the Shelters, further recommendations by Lord Horder's committee, *ibid.* p. 24.

physicians, seldom if ever have any college education; indeed, some have not even completed the high school. In the *National Chiropractic News* for November-December 1940 appears an editorial entitled "Witch-Hunting in Indiana." This rumination was elicited in response to what appears to be a campaign of T. M. Overley, secretary of the Indianapolis Better Business Bureau, looking toward the prosecution under the laws of the state of Indiana of all unlicensed chiropractors practicing in the state. These individuals seek to practice in disregard of such an inconvenient and inconsequential technicality as obtaining a license after presenting to the Board of Registration in Medicine evidence of the educational qualifications required by the Medical Practice Act of Indiana and satisfactorily passing the examination required by law. Mr. Overley, so the editorial states, is "bluenosed" in this campaign "against qualified but unlicensed chiropractors." Were this statement not so pathetic, it would be ludicrous. "Qualified" by whom, for what? Shall cultists be permitted to ignore the applicable healing art licensing law if, in their own estimation, they possess the qualifications required by that law? Is the matter of licensure not a function of the state?

Quoting directly from the editorial:

We asked him [the secretary of the Indianapolis Better Business Bureau] to distinguish and differentiate between the qualified, responsible [unlicensed] practitioner and the unqualified racketeer.

Granting, without admitting, that such a distinction could be drawn, the request for such a distinction itself evidences the unique mentality behind chiropractic thinking. Apparently it is good chiropractic theory to ignore a healing art licensing law, on the ground that such a law applies to the mass of men and to physicians but not to any adherent of this blissfully uninformed cult.

Mr. Overley, because of this campaign against all chiropractors violating the licensing laws of the state, because of his "purblind, bigoted" refusal to take the heat off "qualified but unlicensed chiropractors," is, the editorial remarks (after giving due credit to Gen. Hugh Johnson for originating the phrase), "suffering from halitosis of the intellect." This significant diagnosis, notwithstanding its origin in the General and its acceptance by the chiropractors, is just as scientific as chiropractic itself. The editorial implies that Mr. Overley's efforts to suppress the unlicensed practice of chiropractic must be bearing some fruit. However unfortunate from the chiropractic point of view, this consummation is distinctly in the public interest. Indeed, the public owes a debt of gratitude to Mr. Overley and the Better Business Bureau for their earnest campaign to make effective the medical practice act and for their self sacrifice in exposing themselves to the type of attack that such a campaign inevitably stimulates.

### THE RECORD OF A BLOOD DONOR

The value of human blood and plasma for transfusion in certain diseases is now well established; its lack of specific value for other conditions may not be so well known to physicians and to the public. The effects of the injection of nonspecific protein and of the materials contained in blood and plasma may be sufficient in themselves to develop nonspecific benefits which may cause false impressions of values. This exceedingly brief evaluation of blood transfusion is by way of introduction to a problem created by the drama associated with the donation of human blood for medical purposes. The creation of blood banks and serum centers, and the efforts now being made to secure donation of blood from hundreds of thousands of persons, will in time establish routines which may make such records as that which follows impossible.

In the *Cosmopolitan* magazine for November 1940 appeared an article relative to Mrs. Rose McMullin, who in 1935 apparently permitted herself to be infected with *Staphylococcus aureus* in order that she might develop antibodies. It had been decided to use her blood for transfusion in the case of her niece, who was suffering from an infection with *Staphylococcus aureus*. The physicians in the Hahnemann Hospital in Philadelphia, according to the article, utilized this procedure on her suggestion. They took blood from Mrs. McMullin on several occasions and injected it into the niece. The niece recovered. Then in 1938, it is said, Mrs. McMullin responded to a request for blood to be used for a boy who was dying from *Staphylococcus aureus* infection in Delaware County, Pa. Some time later came an appeal from Chester, Pa., and again Mrs. McMullin responded. By this time apparently she began to be known as the "golden lady," probably because of the *Staphylococcus aureus* infection. She is also occasionally referred to as "the darling of the American Legion," since the American Legion is participating in the campaign to secure blood for transfusion for the military services.

According to the article in the *Cosmopolitan* magazine, "Mrs. McMullin had donated her magical help free, refusing the usual donor's fee. All she accepted was traveling expenses." Then Gabriel Heatter put Mrs. McMullin on his program. From that time requests for her blood began to come in great numbers, not only for cases of *Staphylococcus aureus*, but also for infections with *Streptococcus viridans*, from patients with leukemia and for other conditions. It would seem according to the article in the *Cosmopolitan* magazine, that Mrs. McMullin has a heavy file of letters of gratitude from physicians and that "she has given over 26,000 cubic centimeters of her golden life stream" [sic].

In the files in the headquarters office of the American Medical Association, information has accumulated which must be placed with that in the *Cosmopolitan*. First is a letter from a physician in Johns Hopkins Hospital who

inquired about the use of her blood for a case of myeloid leukemia. In this instance, the doctor writes, the parents of the child had been informed by Mrs. McMullin's agent that she had recovered from leukemia and that her blood contained the proper neutralizing bodies. It was stated that she would ask no fee but merely \$500 for her expenses. References were given to two physicians who were said to have used her blood for cases of leukemia, but specific inquiry revealed that the blood had not been of the slightest use in these cases.

Another letter from a physician in Newark indicates that her blood was offered for a case of *Streptococcus viridans* infection, with a request for \$300 to cover expenses. A third letter from a physician in Louisiana concerned a patient with subacute bacterial endocarditis. Next comes a report from a physician in New York, enclosing extended correspondence with Mrs. McMullin, begun because the father of a 6 year old girl with lymphogenous leukemia asked that a transfusion be made with the blood of Mrs. McMullin. An extended correspondence indicates that Mrs. McMullin did not insist that her blood would help a patient with leukemia but said she would take a while to build up her blood so that it could be used in that direction. In October 1940 her blood was examined by a New York physician, who found that she had a moderate anemia; he refused to use her blood until she could get a certificate from her own physician that it would be satisfactory.

Next comes a communication from a physician in Pennsylvania late in December. A farmer's boy in his community had *Streptococcus viridans* infection with subacute bacterial endocarditis. In this instance the *Philadelphia Inquirer*, having learned of the case, telephoned offering the services of Mrs. McMullin, who it seems was at that time in Oklahoma City giving her blood to another patient with *Streptococcus viridans* infection. The physician had difficulty locating Mrs. McMullin and after correspondence discovered that her blood was not of the right type. She was, however, apparently making a series of visits to various communities for the distribution of her blood. A physician from Missouri and another from Alabama who had experiences with Mrs. McMullin wrote that she states she will give her blood just for "expenses" but that her expense sheets "would make our national debt pale into pauper figures."

There comes also at this time a letter from a physician in Missouri who requested that Mrs. McMullin send her serum in a small bottle, having it taken by one of the blood banks in New York. The price asked for these bottles of serum was \$100 per bottle. The amounts which came in these bottles varied from 210 to 51 cc. of serum.

In the case of one boy with streptococcal endocarditis, Mrs. McMullin provided enough blood for seven transfusions of approximately 200 cc. each over a period of two weeks. When the patient failed to

respond, she insisted that the physician discontinue the sulfathiazole. This he did, but the fever went upward again immediately, so the sulfathiazole was again administered, whereupon there occurred an immediate drop in the temperature.

This is the record to date of a widely publicized blood donor. It provides many strange sociologic and psychologic facets. The report indicates the need for some type of control over this form of medical activity.

## Current Comment

### NEW TYPE OF VIRUS FROM EPIDEMIC INFLUENZA

In February and March 1940 an epidemic of acute respiratory disease simulating epidemic influenza occurred at Irvington House, a convalescent home for children with rheumatic heart disease. Reports of an investigation of this epidemic by Francis<sup>1</sup> indicate that neutralization tests done with serums obtained from early cases failed to reveal any rise in antibody titer against the standard PR8 strain of influenza virus. One of the ferrets inoculated with throat washings from one of the patients (Lee) developed some respiratory distress. At necropsy on the sixth day, mild bluish discoloration of the lower lobe of the left lung was disclosed. Other investigations indicated clearly, according to the criteria established in 1937 by Francis and his co-workers, that this outbreak of respiratory disease was not associated with the virus of influenza (PR8). However, the serums of Irvington House patients which had not exhibited a rise in convalescent titer against the standard PR8 strain were tested against a 10 per cent mouse lung suspension containing the new virus called the Lee virus. In short, the investigations definitely established the causal association of the Lee virus with the Irvington House epidemic and demonstrated a complete lack of serologic relationship between that virus and strains of virus isolated from other epidemics of influenza. Similar observations were made with regard to the January and February 1940 epidemic throughout the Southeastern portion of the United States. Clinically both epidemics were indistinguishable from mild epidemics caused by the PR8 strain. Of additional interest were the studies on the widespread epidemic of 1936. Serums—which had been kept in storage—from two patients typically involved in that epidemic were tested against both the PR8 and the Lee virus. Pronounced rises of titer against the Lee virus occurred but not against PR8. In consequence, this epidemic four years earlier was apparently also due to virus of the Lee type. These observations lead to important conclusions: the epidemics of 1936-1937 and 1938-1939 have been shown to be caused by influenza virus of the usual variety, while those of early 1936 and 1940 are of the Lee type. Clinically the two are indistinguishable but the two infections apparently present completely serologically

1. Francis, Thomas, Jr.: A New Type of Virus from Epidemic Influenza, *Science* 92: 405 (Nov. 1) 1940.

distinct entities and independent cycles. Until further differential studies are made, however, they should both be considered epidemic influenza caused by virus of different serologic types. Following a classification recently suggested, the established form of epidemic influenza (caused by the PR8 virus) is classed influenza A, and outbreaks caused by virus of the Lee type are to be designated influenza B.

#### BLOOD PLASMA FOR GREAT BRITAIN

On Nov. 4, 1940 Dr. DeWitt Stetten,<sup>1</sup> chairman of the board of medical control and vice president of the board of trustees of the Blood Transfusion Betterment Association, reported to the committee on public health relations of the New York Academy of Medicine on the blood plasma for Great Britain project. The first meeting to consider this enterprise took place on June 12, 1940. The Red Cross agreed to advance \$25,000 with an additional grant of \$5,000 and to conduct the publicity necessary to obtain volunteer donors. The call for donors was made through the press, over the radio and by the wide distribution of descriptive posters and pamphlets. The response was immediate and enthusiastic. From August 15 to November 1, 6,961 volunteer donors were sent to the eight cooperating hospitals. To this number 404 were added by the hospitals themselves. Of this total of 7,365, 381, or 5.17 per cent, were rejected for various reasons. The blood of 75 donors (1.07 per cent) was rejected because of positive Wassermann tests for syphilis. Up to and including Nov. 1, 1940, 950 liters of plasma saline solution was released to the Red Cross as sterile and ready for shipment. Preference was given to plasma rather than to serum, and to liquid rather than to dried plasma. To date 30 liters, or 3.15 per cent, of the solution was lost because of contamination. By the first of November 747 liters of plasma saline solution was shipped abroad. The rule was adopted that the age of a donor must be over 21 and under 60 years, the minimum systolic blood pressure 110 and the hemoglobin 80 per cent. Blood with even the slightest positive test for syphilis is discarded. Fifty cc. of a 5 per cent solution of sodium citrate was added to 500 cc. of blood. A 1:10,000 solution of merthiolate is added for its bacteriostatic and bactericidal effect. To keep the plasma from becoming too viscous and to prevent the precipitation of fibrinogen, 50 per cent dilution with physiologic solution of sodium chloride is practiced. The 1 liter Baxter plasma-vac bottle was selected as container. The pooled plasma and the plasma saline solutions were kept until shipment at a temperature of from 3 to 5 C. Bacteriologic studies were first made at the various hospitals and were simultaneously checked at the laboratory of Dr. Frank Meleney by cultures made on the third, seventh and fourteenth days. Toxicity was determined by animal tests. The advisability of the conversion of the plasma into serum by precipitating out the fibrinogen with a calcium salt is now being considered. The success of the enterprise is due largely to the voluntary service on the part of

various specialists in the field of blood transfusion, the doctors, the nurses and hospital personnel, all of whom offered their services gratuitously. The appointment on October 1 of Dr. Charles R. Drew, assistant professor of surgery at Howard University College of Medicine, as salaried medical supervisor was a wise step. A number of related problems are being investigated. One of them is the development of a satisfactory method of drying plasma or serum. This, Dr. Stetten believes, will be the eventual solution of the problem because of the much greater stability of the dried product, its smaller bulk, the relative simplicity of packing, storing and transporting it and the much lesser danger of loss from breakage. The importance of the development of a system of mass production of blood substitutes to our own defense program is evident.

#### "CUTTING THE DOCTOR'S BILL TO FIT"

Physicians were cognizant of the problem of providing good medical service to the indigent and low income classes long before social reformers began to take the problem into politics. And the medical profession did something about it! Fred DeArmond, "Cutting the Doctor's Bill to Fit," in *Nation's Business* for November, is impressed by two different types of approach:

Doctors try a new procedure on a guinea pig first. If it works, they use it on a patient.

... Social reformers ... experiment on the whole nation and, if there isn't too much revolt, they then test the procedure on a guinea pig.

Between 1932 and 1938 more than 200 county medical societies entered into agreements with relief authorities to provide medical care for the indigent. In twenty-six states, county medical societies cooperated with the Farm Security Administration in trying out plans to provide medical service to the low income classes. Not all of these plans were a success and physicians did not expect them to be. They were frankly experiments. Organized medicine also experimented with medical service bureaus through which the indigent were "filtered" to the proper source of medical service and which made arrangements for convenient postpayment plans. Some of these experiments failed, but something was learned from each of them. And the whole nation was not used as a guinea pig. In a number of states, prepayment plans are now being introduced on a statewide basis. Sometimes an enabling act of the state legislature has been required. The state plans are not all alike. Michigan, California and New York, where the plans have actually gone into operation, differ in a number of minor details. In Wisconsin several plans were tested. The state medical society in every case is watching not only its own plan but those of all other states engaged in such an experiment. Unlike many social reformers and critics, the medical profession will abandon any of the features of a plan that prove unsatisfactory or may adopt any more successful features from other states. One difficulty seems to be common to all these plans. The public is not particularly enthusiastic about prepayment for medical service. There is no evidence that the citizens of this country are yearning for any universal compulsory system.

1. Stetten, DeWitt: The Blood Plasma for Great Britain Project. *Bull. New York Acad. Med.* 17: 27 (Jan.) 1941.

# MEDICAL PREPAREDNESS

*In this section of The Journal each week will appear official notices by the Committee on Medical Preparedness of the American Medical Association, announcements by the Surgeon Generals of the Army, Navy and Public Health Service, and other governmental agencies dealing with medical preparedness, and such other information and announcements as will be useful to the medical profession.*

## SIX THOUSAND FIVE HUNDRED ARMY GENERAL HOSPITAL BEDS

Six large general hospitals providing a total of 6,500 beds which are being built by the army are expected to be ready for use March 1, the War Department has announced. The hospitals are to be located in Atlanta, Ga., Charleston, S. C., New Orleans, Fort Benjamin Harrison, Indiana, Santa Barbara, Calif., and Vancouver, Wash. The total cost will be \$8,879,969. New hospital facilities have also been authorized for Fort Francis E. Warren, Wyoming, costing about \$311,500, consisting of a cantonment type hospital of two hundred beds on a three hundred bed plan.

## EXAMINATION FOR COMMISSIONS IN NAVY MEDICAL CORPS

Applications for commissions as medical officers in the U. S. Navy are now being received in the Bureau of Medicine and Surgery, Navy Department, Washington, D. C. Examinations for entrance into the Medical Corps of the regular Navy will be held on May 12 to 15, inclusive, 1941, at all of the larger naval hospitals, including those at Chelsea (Boston), Mass., Brooklyn, Philadelphia, Portsmouth (Norfolk), Va., Great Lakes, Ill., Charleston, S. C., Pensacola, Fla., San Diego, Calif., Mare Island, Calif., Puget Sound (Bremerton), Wash., and at the Naval Medical Center, Washington, D. C. Successful candidates from this examination will receive their appointments approximately two months from the date of the examination.

Applicants are required to be citizens of the United States between 21 and 32 years of age at the time of appointment, graduates of a class A medical school, and to have completed at least one year of intern training in a hospital accredited for intern training by the Council on Medical Education and Hospitals of the American Medical Association. They are required to be physically qualified and to demonstrate their professional qualifications by written, oral and practical examinations embracing the subjects of general medicine, general surgery, obstetrics and gynecology, and preventive medicine and jurisprudence. The physical and professional examinations usually require from three to four days for completion.

Successful candidates are commissioned as assistant surgeons with the rank of lieutenant (junior grade) in the Medical Corps of the Navy. An officer of this rank receives compensation of \$2,699 a year if he has no dependents and \$3,158 a year if he has dependents.

A "Circular for the Information of Persons Desiring to Enter the Medical Corps of the United States Navy," including data pertaining to physical requirements, promotion and retirement, may be obtained by addressing a request to the Surgeon General of the Navy, Navy Department, Washington, D. C.

## NAVY PLACES RESEARCH UNIT ON ACTIVE DUTY

The assignment to active duty of all officers and enlisted personnel of Laboratory Research Unit No. 1 of the U. S. Naval Reserve, for the purpose of conducting intensive research on methods of improving the immunizing capacity of influenza virus vaccine, has been announced by Secretary of the Navy Knox. The University of California has offered the use of the laboratory facilities of the university's medical school at Berkeley for this research. Cooperation with the Rockefeller Foundation, which supports the Influenza Laboratory at that location, and the California State Department of Health, has been requested. Commander A. P. Krueger, M. C., U. S. N. R., head of the Department of Bacteriology of the University of California Medical School, organized this laboratory research unit and will be in charge of the project, assisted by Lieut. Robert A. Hicks, U. S. N. R., of Tucson, Ariz., and nine specially qualified hospital corpsmen of the Naval Reserve. In conducting this research, it is planned to investigate all types of influenza occurring in Naval and Marine Corps personnel throughout the entire service. Laboratory Research Unit No. 1 was organized in 1934.

## A SECOND FIELD ARMY LABORATORY

About February 10 a second field army laboratory will be set up at Fort Sam Houston, Texas, for training purposes similar to the army laboratory set up at the same station recently. It will be a semimobile unit consisting of a stationary central laboratory and three smaller mobile laboratories housed in trailers. The laboratory of this kind now in operation has forty-five enlisted men attached to it and, of the thirty privates and privates first class, eighteen hold specialists' ratings; there is a master sergeant who is a senior laboratory technician, three technical sergeants providing a senior laboratory technician for each mobile unit, three staff sergeants, seven sergeants and one first sergeant. Eleven officers are assigned to the laboratory. As yet no commanding officer has been assigned to the new unit.

## DR. PARRAN TO STUDY CIVILIAN DEFENSE PROBLEMS

Dr. Thomas A. Parran, Surgeon General, U. S. Public Health Service, Washington, D. C., will serve on a four man commission to study civilian defense problems in Britain. Dr. Parran sailed for London January 18, to remain abroad about one month. The commission will study, under orders from the War Department and the National Defense Advisory Commission; problems of health, transportation, utilities and child evacuation in a country under bombardment.



# ARMY RESERVE OFFICERS ORDERED TO ACTIVE DUTY

## WAR DEPARTMENT

The following additional medical reserve officers had been ordered to active duty by direction of the War Department, Washington, D. C., up to January 17:

BECK, Morton Sidney, 1st Lieut., Philadelphia.  
FAIER, Samuel Z., 1st Lieut., Omaha.  
HOLDER, Hall G., Captain, San Diego, Calif.  
HUNTER, Robert Charles, 1st Lieut., Washington, D. C.  
JORGENSEN, Philip Burnell, 1st Lieut., Mosinee, Wis.

## FIRST CORPS AREA

The following additional medical reserve officers had been ordered to extended active duty with the regular army by the Commanding General, First Corps Area, since January 10. The First Corps Area comprises the states of Maine, Vermont, New Hampshire, Rhode Island, Massachusetts and Connecticut.

ADLER, Hyman, 1st Lieut., Brooklyn, Fort McClellan, Ala.  
BATTISTA, Vincent J., 1st Lieut., New York, Fort McClellan, Ala.  
BIRNBAUM, Morris S., 1st Lieut., New York, Fort McClellan, Ala.  
BOGEN, Ben, 1st Lieut., Brooklyn, Fort McClellan, Ala.  
BURSEN, Earl P., 1st Lieut., Brooklyn, Fort Ontario, N. Y.  
COHN, Samuel H., 1st Lieut., Hartford, Conn., Fort Benning, Ga.  
COHN, Stanley H., 1st Lieut., Brooklyn, Fort Dix, N. J.  
DALY, Joseph P., 1st Lieut., Long Island City, N. Y., Fort Hamilton, N. Y.

## SECOND CORPS AREA

The following additional medical reserve officers had been ordered to extended active duty by the Commanding General, Second Corps Area, up to January 17. The Second Corps Area comprises the states of New York, New Jersey and Delaware.

BLUMENTHAL, Basil, 1st Lieut., Washington, D. C., General Dispensary, U. S. Army, Baltimore.  
BRADEN, Frank Robert, Jr., 1st Lieut., Coraopolis, Pa., Camp Blanding, Fla.  
BUTTERMORE, Ralph Morgan, 1st Lieut., Pittsburgh, Pa., Fort Eustis, Va.  
COCKERHAM, Howard Lea, Jr., 1st Lieut., Baltimore, Fort Belvoir, Va.  
CORSELLO, Whitney Carl, 1st Lieut., Pittsburgh, Fort Benning, Ga.  
FISH, Henry, 1st Lieut., Scranton, Pa., Camp Lee, Va.  
HADDEEN, Thomas Miles, 1st Lieut., Saltsburg, Pa., Camp Shelby, Miss.  
HARBATER, Melvin I., 1st Lieut., Forest Hills, L. I., N. Y., Camp Upton, N. Y.  
HEINBACH, Wilfred Frances, Jr., 1st Lieut., Reading, Pa., Indiantown Gap, Pa.  
HIRSCH, Lucien, 1st Lieut., Brooklyn, Camp Livingston, La.  
HOROWITZ, Alexander S., 1st Lieut., Jersey City, N. J., Camp Livingston, La.

## THIRD CORPS AREA

The following additional medical reserve officers had been ordered to extended active duty by the Commanding General, Third Corps Area, up to January 17. The Third Corps Area comprises the states of Pennsylvania, Virginia, District of Columbia and Maryland.

BLAZINA, William Marion, 1st Lieut., McKeesport, Pa., New Cumberland, Pa.  
CLELAND, Charles Edward, Captain, Kane, Pa., Carlisle Barracks, Pa.  
COFFMAN, Milton Buell, Lieut. Col., Richmond, Va., Army Medical Center, Washington, D. C.  
DEAN, James Seay, Captain, Pennhurst, Pa., New Cumberland, Pa.  
DIXON, Charles Warren, Major, Export, Pa., Camp Pendleton, Va.  
ECKHARDT, John Carl, Lieut. Col., Washington, D. C., Fitzsimons General Hospital, Denver.  
FEINMAN, Jack Irwin, 1st Lieut., Philadelphia, Fort McClellan, Ala.  
HIXSON, Clayton Howard, Major, Chevy Chase, Md., Camp Lee, Va.  
IMBRIGLIA, Joseph Ettore, 1st Lieut., Philadelphia, Fort McClellan, Ala.

## FOURTH CORPS AREA

The following medical reserve officers had been ordered to active duty up to January 10 by the Commanding General, Fourth Corps Area, comprising Tennessee, North Carolina, South Carolina, Alabama, Georgia, Mississippi, Florida and Louisiana.

DASPIT, Dudley, Jr., 1st Lieut., Houma, La., Fort McClellan, Ala.  
DERRICK, Clifton J., 1st Lieut., West Palm Beach, Fla., Fort McClellan, Ala.  
DOWELL, Carr T., Jr., 1st Lieut., Baton Rouge, La., Fort McClellan, Ala.

MATLIN, Edwin, 1st Lieut., New York.  
PELTON, Bernard Lynn, 1st Lieut., Toledo, Ohio.  
SINGE, Donald Clemenz, Captain, Bethesda, Md.  
SLOCUM, Donald Barclay, 1st Lieut., Eugene, Oregon.  
SUTULA, Stanley Joseph, 1st Lieut., Washington, D. C.  
WALDRON, John Francis, 1st Lieut., South Orange, N. J.  
WHITAKER, Lawson Spires, 1st Lieut., Washington, D. C.  
WOLFF, Herman, 1st Lieut., Lynchburg, Va.  
ZUCKERMAN, Sidney N., 1st Lieut., San Francisco.

DANISH, Louis J., 1st Lieut., Hollis, L. I., N. Y., Fort McClellan, Ala.  
DIAMOND, Bernard, 1st Lieut., Brooklyn, Camp Livingston, La.  
ERNST, Carl C., 1st Lieut., Great Neck, N. Y., Camp Shelby, Miss.  
ERTEL, Harry, 1st Lieut., Jackson Heights, N. Y., Fort McClellan, Ala.  
FEIGENBAUM, Harry A., 1st Lieut., Brooklyn, Camp Edwards, Mass.  
FINK, Benjamin, 1st Lieut., Brooklyn, Fort McClellan, Ala.  
GAMSO, Rafael R., 1st Lieut., Brooklyn, Camp Livingston, La.  
GARBER, Israel E., 1st Lieut., Mattapan, Mass., Carlisle Barracks, Pa.  
GOODKIN, George, 1st Lieut., New York, Camp Livingston, La.  
HAHN, Joseph G., 1st Lieut., Brooklyn, Fort Devens, Mass.  
LA-TAIF, C. George, 1st Lieut., New Milford, Conn., Carlisle Barracks, Pa.  
MELLONE, John A., 1st Lieut., Bristol, R. I., Fort Ethan Allen, Vt.  
SCHILLER, Israel A., Captain, Brooklyn, Induction Station, Manhattan, N. Y.  
SMITH, Charles S., Major, New Haven, Conn., Fort Devens, Mass.

HYMAN, Aaron, 1st Lieut., New York, Camp Livingston, La.  
JURNOVE, Donald S., 1st Lieut., New York, Camp Livingston, La.  
KARPEL, Saul, 1st Lieut., New York, Camp Livingston, La.  
KLASSON, David H., 1st Lieut., Brooklyn, Camp Livingston, La.  
KLOPP, John Benneville, Major, Chester, Pa., Headquarters Company, Washington, D. C.  
KRENTZ, Benjamin E., 1st Lieut., New York, Camp Livingston, La.  
LEVINSON, David Julius, 1st Lieut., Pittsburgh, Camp Shelby, Miss.  
MAFREDI, Joseph J., 1st Lieut., New York, Camp Livingston, La.  
McMASTER, Gilbert Brown, 1st Lieut., Pittsburgh, Camp Blanding, Fla.  
MILHOLLAND, Arthur Vincent, 1st Lieut., Baltimore, Fort Belvoir, Va.  
NOVALIS, Nicholas A., 1st Lieut., Long Island City, N. Y., Camp Livingston, La.  
PASSARELLI, Arthur Francis, 1st Lieut., Washington, D. C., Fort Story, Va.  
PINCUS, Morris H., 1st Lieut., Brooklyn, New York General Dispensary, U. S. Army, New York.  
SCHEINBERG, Louis, 1st Lieut., Brooklyn, Fort Hancock, N. J.  
SHREARER, Thomas P., 1st Lieut., New York, Fort Dix, N. J.  
THUCKENMILLER, Roy, Major, Freeland, Pa., Camp Lee, Va.  
VASSOS, George A., Jr., 1st Lieut., New York, Fort Dix, N. J.  
WIRTH, Herman E., 1st Lieut., Brooklyn, Induction Station, Queens, New York.  
ZEHNER, David E., 1st Lieut., Brooklyn, Fort McClellan, Ala.

JOHNSTON, Clarence Frederick, 1st Lieut., Baltimore, Denver.  
KOHN, David Francis, 1st Lieut., Mount Pocono, Pa., Fort McClellan, Ala.  
KOLMER, George August Leonard, Major, Salem, Va., Medical Field Service School, Carlisle Barracks, Pa.  
MACKOWIAK, Stephen Casimir, 1st Lieut., Dundalk, Md., Fort McClellan, Ala.  
MAINZER, Francis Stanislaus, Major, Huntingdon, Pa., Army Medical Center, Washington, D. C.  
MANGES, John Paul, 1st Lieut., Scotland, Pa., Fitzsimons General Hospital, Denver.  
McNITT, Henry John Russell, Major, Washington, D. C., Denver.  
MONTGOMERY, Robert Sterling, 1st Lieut., South Hill, Va., Fort Belvoir, Va.  
MUIR, Bennett W., 1st Lieut., Baltimore, Denver.  
PLESSET, Marvin Robert, 1st Lieut., Pittsburgh, Indiantown Gap, Pa.  
PAGE, Bernard Anthony, 1st Lieut., Harrisburg, Pa., Denver.  
SAYLOR, Lloyd Elwood, 1st Lieut., Baltimore, Fort McClellan, Ala.  
SOLOSKO, Alexander, Captain, Salisbury, Pa., Camp Pendleton, Va.  
SUGERMAN, Joseph Richard, 1st Lieut., Pittsburgh, Denver.  
WALKER, Gale Havard, Captain, Polk, Pa., Fort George G. Meade, Md.

GOLDSMITH, Edward F., Jr., 1st Lieut., Toulminville, Ala., Fort McClellan, Ala.  
JERVEY, Allen Jones, Jr., 1st Lieut., Tryon, N. C., Fort McClellan, Ala.  
JOHNSON, Roy L., 1st Lieut., Douglas, Ga., Fort McClellan, Ala.  
LOGAN, James G., 1st Lieut., Natchez, Miss., Fort McClellan, Ala.  
LONG, Thomas W., 1st Lieut., Newton, N. C., Fort McClellan, Ala.  
MOSLEY, Robert S., 1st Lieut., Miami, Fla., Fort McClellan, Ala.  
O'DELL, John C., Jr., 1st Lieut., Jacksonville, Fla., Camp Blanding, Fla.  
O'NEAL, Buford L., 1st Lieut., Shreveport, La., Fort Jackson, S. C.  
PAINTER, William W., 1st Lieut., Spartanburg, S. C., Fort McClellan, Ala.

**Orders Revoked**

The officers whose names are printed in the adjoining column, and who were previously reported, have been relieved from duty or their orders have been revoked.

**EIGHTH CORPS AREA**

The following additional medical reserve officers had been ordered to active duty by the Commanding General, Eighth Corps Area, up to January 11. The Eighth Corps Area comprises the states of Colorado, Arizona, New Mexico, Oklahoma and Texas.

ARMSTRONG, Hiram E., 1st Lieut., Pueblo, Colo., Fort Bliss, Texas.  
ARONOFF, Billie L., 1st Lieut., Dallas, Texas, Fort Bliss, Texas.  
ARRINGTON, John Hodge, Jr., 1st Lieut., Wichita Falls, Texas, Station Hospital, Fort Sam Houston, Texas.  
BICKLEY, Estill T., 1st Lieut., Corpus Christi, Texas, Station Hospital, Fort Sam Houston, Texas.  
BUCHTEL, Henry A., 1st Lieut., Denver, Station Hospital, Fort Sam Houston, Texas.  
BUSH, Walter H., 1st Lieut., Dallas, Texas, Fort Bliss, Texas.  
COCKRELL, John A., Captain, Houston, Texas, Fort Crockett, Texas.  
CURTIS, Wildcliffe R., Captain, El Paso, Texas, Fort Bliss, Texas.  
DOZIER, Fred S., 1st Lieut., Dallas, Texas, Station Hospital, Fort Sam Houston, Texas.  
EMENHISER, Lee K., Captain, Oklahoma City, Station Hospital, Fort Sam Houston, Texas.  
FARNESSE, O. J., 1st Lieut., Tucson, Ariz., Fort Bliss, Texas.  
FRENCH, A. James, 1st Lieut., Ann Arbor, Mich., Station Hospital, Fort Sam Houston, Texas.  
FRISSELL, Ben P., Captain, Phoenix, Ariz., Fort Bliss, Texas.  
HUGHES, Raymond P., 1st Lieut., El Paso, Texas, Station Hospital, Fort Sill, Okla.  
IRELAND, Paul M., Captain, Pueblo, Colo., Station Hospital Fort Sam Houston, Texas.  
JOHNSTON, Lawrence Walton, 1st Lieut., Terrell, Texas, Station Hospital, Fort Sam Houston, Texas.  
JONES, Edmund D., Captain, Beaumont, Texas, Fort Bliss, Texas.  
MASON, Porter K., 1st Lieut., Dallas, Texas, Station Hospital, Fort Sam Houston, Texas.  
MITCHELL, Holland C., Captain, San Antonio, Texas, Station Hospital, Fort Sam Houston, Texas.  
PATTERSON, Casey E., 1st Lieut., Dallas, Texas, Station Hospital, Fort Sam Houston, Texas.  
PERRY, James H., 1st Lieut., Fredericksburg, Texas, Fort Bliss, Texas.

**NINTH CORPS AREA**

The following additional medical reserve officers had been ordered to extended active duty by the Commanding General, Ninth Corps Area, up to January 18. The Ninth Corps Area comprises the states of Washington, Montana, Oregon, Nevada, Utah, California and Idaho.

ACKERMAN, Frederick F., 1st Lieut., Seattle, Fort Lewis, Wash.  
ALSBERG, Marden A., 1st Lieut., Glendale, Calif., Nacimiento, Calif.  
BASSETT, John W., 1st Lieut., San Diego, Calif., 7th Division, Camp Ord, Calif.  
BISCHOFF, George H., 1st Lieut., Boise, Idaho, Buckho Ranch, March Field, Calif.  
CANNON, Espey F., 1st Lieut., Salt Lake City, Fort Douglas, Utah.  
CLAWSON, Thomas A., Major, Salt Lake City, Fort Douglas, Utah.  
DANIELE, Joseph A., 1st Lieut., Hollywood, Calif., Buckho Ranch, March Field, Calif.  
DUNCAN, John J., 1st Lieut., West Los Angeles, Calif., Buckho Ranch, March Field, Calif.

CANIPELLI, Edward, 1st Lieut., Jacksonville, Fla.  
CHERRY, James H., 1st Lieut., Asheville, N. C.  
HOUSER, Frank M., 1st Lieut., Macon, Ga.  
NEVANS, Herman B., 1st Lieut., Livingston, Tenn.  
SAMS, Frank H., 1st Lieut., Reynolds, Ga.  
WACHTEL, Leo M., Jr., 1st Lieut., Jacksonville, Fla.  
YOUNG, Henry D., Jr., 1st Lieut., Bushnell, Fla.

POWER, Paul H., Captain, Waco, Texas, Fort Bliss, Texas.  
SANGER, Welborn W., 1st Lieut., Oklahoma City, Okla., Station Hospital, Fort Sam Houston, Texas.  
SCALES, John G., Captain, Dallas, Texas, Fort Bliss, Texas.  
SIMMONS, Lillard Nolan, 1st Lieut., Wichita Falls, Texas, Station Hospital, Fort Sam Houston, Texas.  
SPILLANE, John H., Jr., 1st Lieut., Colorado Springs, Colo., Fort Clark, Texas.  
STECKLER, Milton I., 1st Lieut., Houston, Texas, Fort Bliss, Texas.  
STEVENS, Thomas Hood, 1st Lieut., Sulphur Springs, Texas, 45th Division, Fort Sill, Okla.  
STOWERS, Aubrey E., 1st Lieut., Sentinel, Okla., 45th Division, Fort Sill, Okla.  
STUART, Samuel E., Captain, Dallas, Texas, Fort Bliss, Texas.  
STURM, Charles E., Captain, San Antonio, Texas, Station Hospital, Fort Sam Houston, Texas.  
TALLEY, John E., Captain, Hamilton, Texas, 45th Division, Fort Sill, Okla.  
WALKER, Charles E., Jr., Captain, Denver, Station Hospital, Fort Sam Houston, Texas.  
WILKINSON, Robert T., 1st Lieut., Rotan, Texas, Station Hospital, Fort Sam Houston, Texas.  
WILLIS, Raymond S., Captain, Dallas, Texas, Station Hospital, Fort Sam Houston, Texas.  
WILSON, Charles Hugh, 1st Lieut., Oklahoma City, 45th Division, Fort Sill, Okla.

**Orders Revoked**

Orders on the following officers, previously reported, have been revoked:

DOYLE, William H., Captain, Muskogee, Okla.  
HARRISON, Ben F., Jr., 1st Lieut., Dallas, Texas.  
LEDBETTER, William Harry, 1st Lieut., Wichita Falls, Texas.  
LEWIN, Julian R., 1st Lieut., Redvale, Colo.  
MONROE, M. L., 1st Lieut., Jasper, Texas.  
RICHEL, George T., 1st Lieut., Denver.  
SMITH, Haskell, 1st Lieut., Stillwater, Okla.  
SWITZER, Fred D., 1st Lieut., Hugo, Okla.  
VAN SICKLE, Rayburn Jefferson, 1st Lieut., Longview, Texas.

FALK, Harry, Captain, Visalia, Calif., Buckho Ranch, March Field, Calif.  
JANTZEN, Roland R., 1st Lieut., Redding, Calif., Antiaircraft Firing Center, Riverside, Calif.  
JEANS, Virgil E., 1st Lieut., Fresno, Calif., Buckho Ranch, March Field, Calif.  
LOWELL, Lawrence M., 1st Lieut., Astoria, Ore., Fort Stevens, Ore.  
ROGGE, Edgar A., Captain, Seattle, Fort Lewis, Wash.  
WALKER, Ralph J., 1st Lieut., Oakland, Calif., Fort Scott, Calif.  
WEINSTEIN, William, 1st Lieut., Everett, Wash., Camp Clatsop, Ore.  
WELLS, Howard A., 1st Lieut., Redmond, Ore., Fort Lewis, Wash.  
WILMES, Malcolm N., Captain, Woodland, Calif., Office of Corps Area Surgeon, Presidio of San Francisco.  
WOOLCOTT, Floyd L., 1st Lieut., Portland, Ore., Fort Worden, Wash.

**Relieved from Duty**

CARLILE, Thomas B., 1st Lieut., ordered to Fort Lewis, Wash., Dec. 5, 1940, relieved from active duty January 6.  
SHORT, Faulkner A., 1st Lieut., ordered to Fort Worden, Wash., Nov. 14, 1940, relieved from active duty January 16.  
SORENSEN, Edward J., 1st Lieut., ordered to Fort MacArthur, Calif., Dec. 15, 1940, relieved from active duty January 11.

**NAVAL RESERVE OFFICERS ORDERED TO ACTIVE DUTY**

The following additional naval medical reserve officers have been ordered to active duty:

BERNSTEIN, Wilbur B., Lieut. (j. g.), M. C.-V. (G.), New York, 7th Medical Company, Fleet Marine Force, Quantico, Va.  
BLOEMERS, Harms W., Lieut. (j. g.), M. C.-V. (G.), New York, 7th Medical Company, Fleet Marine Force, Quantico, Va.  
DANIELS, Willard F., Lieut. (j. g.), M. C.-V. (G.), Huntington, W. Va., 8th Medical Company, Fleet Marine Force, Quantico, Va.  
DAVIDOFF, Manuel A., Lieut. (j. g.), M. C.-V. (G.), Paw Paw, W. Va., 8th Med. Company, Fleet Marine Force, Quantico, Va.  
DONABEDIAN, George, Lieut. (j. g.), M. C.-V. (G.), New York, 7th Medical Company, Fleet Marine Force, Quantico, Va.  
DUNCAN, Charles S., Lieut. (j. g.), M. C.-V. (G.), Huntington, W. Va., 8th Medical Company, Fleet Marine Force, Quantico, Va.  
FORSYTHE, Richard M., Lieut. (j. g.), M. C.-V. (G.), Vahalla, N. Y., 8th Medical Company, Fleet Marine Force, Quantico, Va.

FRITCHEN, A. F., Lieut. Comdr., M. C.-V. (S.), Decorah, Iowa, Naval Hospital, San Diego, Calif.  
GIESEN, Josef H., Lieut. (j. g.), M. C.-V. (G.), West Haverstraw, N. Y., 8th Medical Company, Fleet Marine Force, Quantico, Va.  
HALEY, Peter A., II, Lieut. (j. g.), M. C.-V. (G.), Charleston, W. Va., 8th Medical Company, Fleet Marine Force, Quantico, Va.  
HANSON, Harry A., Lieut. (j. g.), M. C.-V. (G.), Rochester, N. Y., 8th Medical Company, Fleet Marine Force, Quantico, Va.  
LEES, C. R., Lieut., M. C.-V. (S.), Fort Worth, Texas, Naval Hospital, San Diego, Calif.  
MORRISON, A. A., Lieut., M. C.-V. (S.), Portland, Maine, Naval Hospital, San Diego, Calif.  
MUNCH, Otto L., Lieut. (j. g.), M. C.-V. (G.), Rochester, N. Y., 8th Medical Company, Fleet Marine Force, Quantico, Va.  
PATTERSON, J. K., Lieut., M. C.-V. (G.), Santa Barbara, Calif., Naval Hospital, San Diego, Calif.  
VIECELLI, J. D., Lieut. Comdr., M. C.-V. (G.), San Francisco, Naval Hospital, San Diego, Calif.

# ORGANIZATION SECTION

## MEDICAL LEGISLATION

### MEDICAL BILLS IN CONGRESS

*Bills Introduced.*—S. 165, introduced by Senator Sheppard, Texas, proposes to continue in the service of the Army, Navy, Marine Corps and Coast Guard beyond the term of their enlistment those suffering from service connected disease or injury and in need of medical or hospital care until recovery through such medical care and hospitalization. S. 238, introduced by Senator Sheppard, Texas, provides that Reserve officers, Army of the United States, who were called or ordered into active military service by the federal government for extended service in excess of thirty days on or subsequent to Feb. 28, 1925, other than for service with the Civilian Conservation Corps and who are now disabled from disease or injury contracted or received in line of duty while so employed, shall be entitled to receive the same retirement pay and hospital benefits as are now or may hereafter be provided by law or regulation for officers of corresponding grades and length of service of the Regular Army. S. 341, introduced by Senator Walsh, Massachusetts, proposes to authorize the Secretary of the Navy to establish naval hospitals at the naval air stations at Jacksonville, Fla., Corpus Christi, Texas, and San Juan, Puerto Rico; the submarine base, Coco Solo, Canal Zone; the naval station, Guantanamo Bay, Cuba, and the marine barracks, Quantico, Va. S. 397, introduced by Senator Reynolds, North Carolina, proposes to provide domiciliary, medical and hospital treatment to certain former members of the Army, Navy, Marine Corps and Coast Guard. S. 398, introduced by Senator Reynolds, North Carolina, and H. R. 2524, introduced by Representative Van Zandt, Pennsylvania, propose to provide benefits on account of disability or death due to service in the armed forces of the United States in the event of war. H. R. 81, introduced by Delegate Dimond, Alaska, proposes to authorize the Secretary of the Interior to construct in the territory of Alaska or in the continental United States a hospital for the treatment of the insane of Alaska and of such other classes of persons who are insane or who may require mental treatment as the President may designate for care and treatment in the hospital. H. R. 164, introduced by Representative Voorhis, California, proposes to grant permanent and total disability ratings to veterans suffering from severe industrial inadaptability as a result of war service. H. R. 1076, introduced by Representative Shafer, Michigan, proposes to extend the benefits of the United States Employees' Compensation Act to emergency relief employees suffering from occupational diseases. H. R. 1395, introduced by Representative Green, Florida, proposes to construct a marine hospital in Florida. H. R. 1624, introduced by request, by Representative Rankin, Mississippi, proposes to define the terms "permanent and total" or "total permanent" as "any reasonably permanent impairment or defect of mind or body, or both, which prevents the individual from following a substantially gainful occupation, providing that, without prejudice to any other cause of disability or employability, the permanent loss of the use of both feet, of both hands, or of both eyes, or of one foot and one hand, or of one foot and one eye, or of one hand and one eye, or the loss of hearing of both ears, or the organic loss of speech shall be deemed total permanent disability," wherever such terms are used in laws relating to the payment of compensation or pension to veterans of the World War. H. R. 2226, introduced by Representative Bates, Kentucky, proposes to define misconduct, for compensation and pension purposes, as limited to felonious misconduct. H. R. 2230, introduced by Representative Brooks, Louisiana, provides that any veteran of any war, who was not dishonorably discharged and who is suffering from any disability, disease or defect irrespective of whether service connected or not, shall be entitled to receive outpatient treatment at facilities of the Veterans'

Administration. H. R. 2245, introduced by Representative Cluett, New York, proposes a federal appropriation of \$4,050,000 to construct a veterans' general medical and surgical hospital in one of the counties of Rensselaer, Saratoga, Warren or Washington, in the state of New York, with a capacity of at least one thousand, two hundred beds. H. R. 2283, introduced by Representative McMillan, South Carolina, proposes to extend eligibility for pensions to the widows and children of World War veterans who had disabilities caused or aggravated by examination, hospitalization or medical treatment. H. R. 2299, introduced, by request, by Representative Rankin, Mississippi, proposes to liberalize the benefits for disabled veterans and dependents of deceased veterans. Among other things, the bill provides that any person who served in the military or naval forces of the United States during a recognized campaign or expedition, and who was honorably separated from such service, shall be granted hospitalization, domiciliary care and burial allowances; that retired personnel of the Army, Navy, Marine Corps and Coast Guard, and Fleet Naval and Fleet Marine Corps reservists requiring hospitalization shall be entitled to enter any Army or Navy hospital; that retired enlisted men of the Army, Navy, Marine Corps and Coast Guard when hospitalized or domiciled in either an Army or Navy hospital or United States naval or United States soldiers' home shall be extended such treatment or domiciliary care without cost; and that any veteran of any war who was not dishonorably discharged and who is suffering from any disability, disease or defect, irrespective of whether such disability, disease or defect is service connected, shall be entitled to receive outpatient treatment at facilities of the Veterans' Administration. H. R. 2467, introduced by Representative Izac, California, provides for reciprocal hospitalization in any Army or Navy hospital or domiciliary care in a United States naval or soldiers' home, without cost, to retired or retained personnel of the United States armed forces. H. R. 2475, introduced by Representative May, Kentucky, proposes to prohibit prostitution within such reasonable distance of military or naval establishments as the Secretaries of War or Navy shall determine to be needful to the efficiency, health and welfare of the Army or Navy. H. R. 2601, introduced by Representative Poage, Texas, proposes to create a pension system for adult cripples and for aged citizens. H. R. 2613, introduced by Representative Sheppard, California, proposes a federal appropriation of \$500,000 to construct a veterans' hospital in San Bernardino or Riverside County, Calif., to provide facilities to care for the "increasing numbers of disabled veterans of all wars suffering from diseases of the chest." S. 489, introduced by Senator Capper, Kansas, proposes to amend the Social Security Act by adding a new title under which grants will be made to induce states to embark on a combined program of compulsory and voluntary health insurance. This appears to be the hardy perennial sponsored by the American Association for Social Security through Mr. Abraham Epstein. S. 509, introduced by Senator Murray, Montana, proposes to provide for the general welfare by enabling the several states to make more adequate provisions for the control and prevention of industrial conditions hazardous to the health of employees. The bill proposes an appropriation for the fiscal year ending June 30, 1941 of \$1,000,000, for the fiscal year ending June 30, 1942 of \$2,000,000, for the fiscal year ending June 30, 1943 of \$3,000,000, and thereafter an appropriation sufficient to carry out the purposes of the bill. The administration of this bill will devolve on the Secretary of Labor, who must approve all state plans, and a state plan must provide for its administration by the state labor department or other agency charged with the administration of the general labor laws of the state.

## STATE MEDICAL LEGISLATION

## Arkansas

*Bills Introduced.*—H. J. R. 1 proposes so to amend the state constitution as to authorize the construction and operation of a state charity hospital, to consist of one thousand, one hundred beds, in Pulaski County. H. 2 proposes to authorize the establishment and operation of a state cancer institute in Phillips County for the care and treatment of persons suffering from cancer and unable to pay for necessary care and treatment in a private institution or able only to pay such expenses in part. H. 32 proposes to create a state hospital commission of five members to manage and control all institutions maintained by the state for the treatment of mental illness and nervous diseases, including the treatment of persons who are feeble-minded, epileptic, drug addicts and suffering from psychoses resulting from alcoholism. The bill proposes that any resident of the state who is mentally ill and in need of hospitalization for such illness shall be eligible for admittance to any appropriate state hospital for diagnosis, care and treatment. The bill proposes that the estate of any patient which is financially able to do so must pay in part for the care rendered that patient.

## California

*Bills Introduced.*—S. 204 proposes that any charitable hospital that has used due care in the selection of its employees shall not be liable for the injury or death of any patient caused by the negligence of such employees, regardless of whether the patient pays in whole or in part for the services he receives. S. 226 and A. 308 propose to make incurable insanity a ground for divorce. H. 245 proposes to require every public or private hospital or school of medicine, surgery or osteopathy to pay any intern in its employ not less than \$50 monthly and, in addition, to provide full board and lodging and laundry services and, in the event of illness or injury, to provide medical treatment and hospitalization. A. 208, to amend the workmen's compensation act, proposes that "the term 'physician' or 'practicing physician' shall, at the option of the employer or employee, be construed to include regularly licensed chiropractors and the term 'medical, surgical and hospital services and supplies' shall, at the option of employer or employee, be construed to include services and supplies by regularly licensed chiropractors or chiropractic hospitals." A. 303, to amend the medical practice act, proposes to exempt from the payment of the required annual registration fee a licentiate while (1) engaged in full time active service in the medical corps of the Army, Navy or Marines or in the United States Public Health Service, or (2) "fulfilling his full period of training and active service, whether as a draftee or volunteer, under the Selective Training and Service Act of 1940." A. 380, to supplement the medical practice act, proposes to authorize the revocation or suspension of the certificate of a licentiate who has committed any act constituting or involving lewd conduct, lascivious conduct, immoral conduct or moral turpitude. Assembly Constitutional Amendment 14 proposes a constitutional amendment to enable the legislature to provide for the operation of a statewide lottery, the revenue from which is to be appropriated to the administration and payment of old age benefits and the administration of state hospitals and asylums. A. 413 proposes that the annual directory of licensed physicians which the medical practice act requires the board of medical examiners to compile and distribute shall contain the following additional information: (1) the annual report of the board for the prior year, (2) information relating to other laws of the state and to the United States which the board may determine to be of interest to licentiates and (3) a copy of the California medical practice act.

## Connecticut

*Bill Introduced.*—H. 27 proposes to safeguard the distribution and sale of certain dangerous caustic or corrosive acids, alkalis and other substances by requiring the containers of such articles sold at retail to be labeled with the name of the article, the name and place of the business of the manufacturer, packer, seller or distributor, the word "POISON" in uncondensed gothic capital letters, not less than 24 point size, and directions for treatment in case of accidental personal injury by the substance.

## Indiana

*Bill Introduced.*—S. 24, to amend the workmen's compensation act, proposes, among other things, to require an employer to provide an employee injured in an industrial accident necessary first aid medical and surgical services and all necessary and hospital services thereafter, limited, however, to that which is reasonably required to cure or relieve the effects of industrial injuries. Under the present law the employer is required to furnish such services only during the first ninety days after the occurrence of the industrial accident.

## Iowa

*Bill Introduced.*—S. 2 proposes to condition the issuance of a license to marry on the presentation by each party to the proposed marriage of a physician's certificate stating that, within twenty days prior to the application for a license to marry, the party has been examined and has been found free of syphilis or any stage of that disease whereby it may become communicable. The physician's certificate must be based on a clinical examination and on a standard serologic test for syphilis.

## Kansas

*Bills Introduced.*—H. 1, to amend the osteopathic practice act, proposes (1) to confer on osteopaths the right to practice operative surgery and obstetrics and to administer antiseptics, anesthetics, narcotics and biologics; (2) to provide that after July 1, 1941 applicants for licenses must, in addition to the educational qualifications now required by law, present evidence of the completion of at least one year of preprofessional education of a college grade in a college approved by the board of osteopathic examiners before commencing the study of osteopathy and, after July 1, 1944, present evidence of having completed at least two years of preprofessional education of a college grade; and (3) to permit the board to license without examination applicants who are certificants of the national board of examiners for osteopathic physicians and surgeons. The bill specifically provides that "Each person holding a legal and valid certificate to practice osteopathy in this state at the time of the passage of this act shall without further proof be entitled to receive the certificate to practice as an osteopathic physician and surgeon hereinabove described, and to enjoy the rights and privileges herein provided for a person holding such a certificate." H. 8 proposes to enact a separate naturopathic practice act and to create an independent board of naturopathic examiners to examine and license applicants for such licenses. The bill proposes to describe naturopathy as a "distinct system of healing based upon its own philosophy of health and disease, defined as an art, science, philosophy and practice, following definite physical, chemical, biological, mental and spiritual laws for the restoration and maintenance of health and the correction of bodily disorders without the use of drugs or surgery. For relief and cure it makes use of nature's most beneficent forces and agencies on the theory that under the normal conditions of natural living the body is a self-recuperating organism."

## Massachusetts

*Bills Introduced.*—S. 485, to amend the medical practice act, proposes to add at the end of the section stating the educational qualifications required of applicants for licenses to practice the following: "The board in its examinations of applicants shall have requirements at least as qualifying as the standards of admission recommended by the National Board of Registration in Medicine." S. 498, to amend the old age assistance act, proposes that the old age assistance to be rendered eligible persons "shall include the furnishing of false teeth, eye glasses, hospital and medical services and expenses." H. 804, to amend the workmen's compensation act, proposes to make compensable "heat exhaustion" suffered by a workman in the course of his employment. S. 561, to amend the law regulating the mode in which records must be kept by hospitals supported in whole or in part by contribution from the state or a subdivision thereof and hospitals conducted as public charities, proposes that whenever preexisting hospital records shall have been photographed or microphotographed and the photographs or microphotographs shall have been indexed and filed by the hospital, the person in charge of the hospital, on due notice, may destroy

the original records so photographed or microphotographed, and the photographs or microphotographs shall have the same force and effect as the original records from which they were made. H. 893 proposes that any person, not in an institution, receiving public support, who is in need of the services of a physician may employ any physician who is registered with the department of civil service and that reasonable compensation must be paid such physicians by the town liable for the support of the patient.

#### Nebraska

*Bills Introduced.*—Bill 4 proposes that within thirty days after the birth of any child born with visible congenital deformities the physician, midwife or person acting as midwife in attendance of such birth shall prepare and file with the bureau of vital statistics, through the director of health, a statement setting forth such visible congenital deformity. The present law requires a report under such circumstances to be made to the Child Welfare Bureau at Lincoln or to any other state commission, board or division having supervision of crippled children. Bill 35 proposes, in effect, to exempt chiropractic applicants from the provisions of the basic science act. The bill proposes that chiropractic applicants be examined in the basic sciences by the chiropractic board rather than by the basic science board.

#### New York

*Bills Introduced.*—S. 154 and A. 140, to amend the workmen's compensation act, propose to permit treatment by public hospitals of workmen's compensation cases when the employer or his insurance carrier refuses or neglects to authorize hospital services and proposes to permit an injured employee to select any hospital for care and treatment in such cases in accordance with rules prescribed by the commissioner. A. 189, to amend the law in relation to the examination of donors of blood for transfusion, proposes to permit the physical examination of such donors within thirty days, instead of ten days, as the law now provides, preceding the offering of such blood donation. A. 243 proposes to require the board of education of each city and of each school district maintaining vocational schools to provide in each vocational high school facilities for health service for

the pupils, which health service is to include necessary facilities to afford adequate physical examinations, including roentgenographing of the chest.

#### Ohio

*Bill Introduced.*—H. 51 proposes to authorize the formation of corporations not for profit to establish, maintain and operate voluntary nonprofit medical care plans whereby professional services will be provided at the expense of such corporations to such persons or groups of persons as become subscribers to such plan under contracts which will entitle each such subscriber to certain professional services by duly licensed physicians and surgeons in their offices, in hospitals and in the home. The term "professional services" as used in the bill is not to be construed to include hospital services.

#### Oklahoma

*Bill Introduced.*—H. 104 proposes to repeal the law prohibiting the retail sale and distribution of certain barbituric acid compounds except on the prescription of a licensed physician, dentist or veterinarian.

#### Pennsylvania

*Bills Introduced.*—S. 20 proposes to impose a stated license tax on slot machines or other similar devices of skill or chance. The bill proposes to appropriate the revenue from such taxes to the department of health for crippled children's hospitals. S. 29 proposes to authorize the sexual sterilization of inmates of stated institutions who are feeble-minded or are afflicted with incurable chronic mania or dementia. The bill also authorizes the sexual sterilization of any inmate of a penal institution who has been convicted more than once of a sex crime. H. 42 proposes to require the department of revenue on behalf of any hospital in the commonwealth to collect or enforce payment of any account for hospital services rendered to any person because of injuries sustained in a motor vehicle accident. If such payment cannot be enforced by the department and the injured person or his estate is unable to pay for the hospital care necessary, the hospital bill is to be paid by the commonwealth out of the motor license fund.

## OFFICIAL NOTES

### THE CLEVELAND SESSION

#### Fraternity Meetings

Fraternities and alumni groups which have not already made arrangements for their meetings during the annual session of the American Medical Association in Cleveland, June 2-6, should do so at once, as the available facilities are being reserved rapidly. Groups desiring assistance should write to the chairman of the subcommittee on fraternity and alumni reunions, Dr. Hiram O. Studley, 1422 Euclid Avenue, Cleveland, Ohio. The general chairman of the local committee on arrangements for the annual meeting of the Association is Dr. Clyde L. Cummer, 1422 Euclid Avenue, Cleveland, Ohio.

#### ADDRESSES BY OFFICIAL STAFF

DR. PAUL C. BARTON:

Feb. 20—South Side B'nai Brith, Chicago.

DR. W. W. BAUFER:

Feb. 1—Women Field Army, the American Society for the Control of Cancer, Indiana Division, Indianapolis.

Feb. 11—Texas Junior College Assembly, Texarkana, Texas.

Feb. 11—Rotary Club, Texarkana, Texas.

Feb. 11—Arkansas Assembly, Texarkana, Ark.

Feb. 11—Public meeting, Texarkana, Texas.

Feb. 12—High school assembly, Athens, Texas.

Feb. 12—Literary Club, Athens, Texas.

Feb. 12—Henderson County Medical Society, Woman's Auxiliary, Athens, Texas.

Feb. 13—Lamar County Medical Society, Woman's Auxiliary, Doctors' Day Program, Paris, Texas.

Feb. 14—Two high school assemblies, Paris, Texas.

Feb. 21—Advisory Committee on Child Welfare, National Congress of Parents and Teachers, New York.

Feb. 25-26—Joint Committee on Health Programs in Education of the National Education Association and the American Medical Association, Symposium, Atlantic City, N. J.

DR. MORRIS FISHBEIN:

Feb. 5—Luncheon, National Social Hygiene Day, Chicago.

Feb. 16—National Conference on Medical Service, Chicago.

Feb. 26—Executives Club, Quincy, Ill.

MR. WILLIAM HOLLOWAY JR.:

Feb. 5—Woman's Auxiliary to Peoria Medical Society, Peoria, Ill.

Feb. 16—National Conference on Medical Service, Chicago.

Feb. 17—Chicago Medical Society Woman's Auxiliary, Stock Yards Branch.

Feb. 18—Congress on Medical Education and Licensure, Chicago.

DR. FRANK H. LAHEY:

Feb. 24—Palm Beach County Medical Society, Palm Beach, Fla.

DR. NATHAN B. VAN ETTEN:

Feb. 9—South Side Clinical Society, Chicago.

Feb. 22—Minisink Historical Society, Port Jervis, N. Y.

#### RADIO BROADCASTS

"Doctors at Work" is the title of the sixth annual series of dramatized radio programs being presented by the American Medical Association and the National Broadcasting Company.

The series opened Wednesday, November 13, and will run for thirty consecutive weeks, closing with a broadcast from the

A. M. A. meeting at Cleveland on June 4. The program is scheduled for 10:30 p. m. eastern standard time (9:30 central, 8:30 mountain, 7:30 Pacific time) over the Blue network, other N. B. C. stations and Canadian stations.

The programs are broadcast on what is known in radio as a sustaining basis; that is, the time is furnished gratis by the radio network and local stations, and no revenue is derived from the programs. Therefore local stations may or may not take the programs, at their discretion, except those stations which are owned and operated by the National Broadcasting Company.

Some radio stations may be unable to broadcast the program at the regular scheduled time and may transcribe and broadcast it at another hour or even on another day. It is advisable therefore to verify the time by reference to local newspapers or by telephoning the local Blue network stations.

The programs will dramatize what modern medicine offers the individual in the way of opportunities for better health and the more successful treatment of disease. Incidental to this main theme the programs will explain the characteristics of the different fields of modern medicine and its specialties.

Descriptive posters for local distribution may be had gratis from the Bureau of Health Education, American Medical Association, 535 North Dearborn Street, Chicago. Program titles will be announced weekly in *THE JOURNAL* and monthly in *Hygeia*, the Health Magazine.

Tickets are available for each broadcast. Address the Bureau of Health Education, American Medical Association, 535 North

Dearborn Street, Chicago. Tickets are free, but a stamped self-addressed envelop should accompany requests.

The next three programs to be broadcast, together with their dates and titles, are as follows:

February 5. New Faces For Old.  
February 12. Medical Detective.  
February 19. One Man's Poison.

The following stations are broadcasting "Doctors at Work" as of January 21:

Akron, Ohio	WAKR	Montreal	CFCF
Albany, N. Y.	WABY	New York	WJZ
Atlanta, Ga.	WAGA	Ocala, Fla.	WTMC
Baltimore	WBAL	Orlando, Fla.	WLOF
Bay City, Mich.	WBCM	Plattsburg, N. Y.	WMFJ
Beaumont, Texas	KFDM	Providence, R. I.	WEAY
Birmingham, Ala.	WSGN	Pueblo, Colo.	KGHF
Bridgeport, Conn.	WICC	Salt Lake City	KUTA
Chicago	WENR	Seattle	KJR
Columbia, Mo.	KFRU	Shenandoah Iowa	KMA
Daytona Beach, Fla.	WMFJ	Sioux City, Iowa	KSCJ
Des Moines, Iowa	KSO	Spokane, Wash.	KGA
Dubuque, Iowa	WKBB	Springfield, Ill.	WCBS
Erie, Pa.	WLEU	Springfield, Ohio	WIZE
Flint, Mich.	WFDF	Toledo, Ohio	WTOL
Fort Wayne, Ind.	WOWO	Washington, D. C.	WMAJ
Greenwood, Miss.	WGRM	Youngstown, Ohio	WFMJ
Jackson, Mich.	WIBM	Charlestown, W. Va.	WGKY
Jackson, Miss.	WSLI	Clarksburg, W. Va.	WBLK
Jacksonville, Fla.	WJHP	Dayton, Ohio	WING
Jamestown, N. Y.	WJTN	Fort Worth, Texas	KGRO
Kansas City, Mo.	WREN	Madison, Wis.	WJRB
Lansing, Mich.	WJIM	Reading, Pa.	WRAW
Miami Beach, Fla.	WKAT	Sioux Falls, S. D.	KELO

## WOMAN'S AUXILIARY

### New Jersey

The Woman's Auxiliary to the Atlantic County Medical Society was held, October 18, with Mrs. Anthony G. Merendino presiding. Mr. Frank McBroom spoke on the "Community Chest."

The Woman's Auxiliary to the Hudson County Medical Society opened its season's activities, October 8, at Jersey City. A board meeting was held in the morning and plans for the year's work and social activities were discussed. This was followed by lunch and bridge. Miss Sadie James, executive director of the Jersey City American Red Cross, spoke on the many activities carried on by the chapter and appealed for the cooperation of the members.

Mrs. Louis Viteri presided at the October meeting of the Burlington County auxiliary, at which time past presidents were presented with pins and corsages.

Forty members and guests were present at the October meeting of the Camden County auxiliary, which met at the home of the president, Mrs. L. L. Glover. Guest speaker was Mr. Harry F. Royce, of Haddonfield, a member of the New Jersey state legislature, who talked on "Children of Today in the World of Tomorrow."

The Woman's Auxiliary to the Essex County Medical Society opened the season with a luncheon meeting, October 28, with an attendance of seventy members, three new ones. Mrs. J. Irving Fort, president, presided. Volunteers were called on to work at the Newark City, Newark, Beth Israel, St. Barnabas and Orange (N. J.) Memorial hospitals and the Academy of Medicine, registering visiting physicians at the fall clinical conference, November 27 and 28.

### Tennessee

The Memphis auxiliary met in October with forty-six new members present. An interesting debate on the issues of the presidential campaign was the feature of the program, planned by Mrs. W. T. Pride. Mrs. Thomas Nelson Coppedge and Mrs. Harry Anderson were the speakers.

Dr. Lois Kennedy spoke on "Allergy" at the meeting of the Woman's Auxiliary to the Rutherford County and Stones River Medical Society held recently at "Shadowlawn," the country home of Dr. and Mrs. J. A. Scott. The annual membership tea of the auxiliary to the Nashville Academy of Medicine and the Davidson County Medical Society was held at the home of Mrs. Frank Fessey.

### Washington

The auxiliary to the King County Medical Society held its membership tea in Seattle in October with one hundred and fifty members present. At the September meeting one hundred and seventy-six members were present, and Mrs. R. E. Mosiman, President-Elect of the Woman's Auxiliary to the American Medical Association gave reports of the national meeting in New York.

The auxiliary to the Spokane County Medical Society met in October. Mrs. C. L. Lyon, public relations chairman, gave a report on the national, state and local candidates and how they stood in regard to medicine. Fifteen dollars was voted to the Spokane Community Chest Fund, and plans made to aid several needy families. Units were appointed to help at Red Cross headquarters one day every week. At the September meeting Mrs. G. E. Hoxsey, state president, was the guest speaker.

The auxiliary to the Pierce County Medical Society held a membership tea in October. At the September meeting Mr. A. E. Anderson, executive secretary of the Washington State Medical Association, spoke on legislation in regard to candidates favorable to medicine in both state and county tickets. Mrs. George Nace was appointed chairman of the welfare project to supply reading material and children's clothing to the Lakeview Tuberculosis Sanatorium.

The Walla Walla Valley Medical Society auxiliary met in October. Mrs. G. E. Hoxsey, president of the state auxiliary, spoke. Other speakers were Mrs. H. A. Mount, Dr. Homer Dudley, president of the state medical association, W. T. Laube, attorney for the association, and Arthur Anderson, executive secretary of the association.

The auxiliary to the Yakima County Medical Society met in October. Guest speakers were Mrs. G. E. Hoxsey, president of the state auxiliary, and Mr. Oscar Schuman, who talked on legislative bills of interest to the medical profession. It was reported that a net profit of \$134.70 from a rummage sale had been turned over to the children's ward at St. Elizabeth's Hospital.

The Clark County auxiliary met in October at Vancouver. *Hygeia* contest rules were reported. The guest speaker was Dr. I. C. Munger Jr., president of the Clark County Medical Society, who gave a talk on the present day setup of the medical profession in the army.



## Medical News

(PHYSICIANS WILL CONFER A FAVOR BY SENDING FOR THIS DEPARTMENT ITEMS OF NEWS OF MORE OR LESS GENERAL INTEREST; SUCH AS RELATE TO SOCIETY ACTIVITIES, NEW HOSPITALS, EDUCATION AND PUBLIC HEALTH.)

### CALIFORNIA

**Annual Postgraduate Assembly.**—The seventh annual postgraduate assembly of the College of Medical Evangelists, Los Angeles, was held December 8. Among the speakers were:

Dr. Henry Borsook, Pasadena, Vitamins: Their Place in Nutrition and Therapy.

Dr. Walter Scott Franklin, Santa Barbara, External Diseases of the Eye with Differential Diagnosis in Conjunctivitis, Iritis and Glaucoma.

Karl F. Meyer, Ph.D., San Francisco, The General Practitioner and Virus Infections of the Central Nervous System.

Drs. Burrell O. Raulston and Harold J. Magnuson, Los Angeles, Treatment of Early Syphilis by the Continuous Drip Method.

Dr. Harold Lincoln Thompson, Los Angeles, Traumatic Perforation of the Intestine, with Report of Cases.

A symposium on the role of vasodilator, vasospastic and antispasmodic drugs in cardiac, gastrointestinal, genito-urinary and peripheral vascular disturbances was presented by Drs. William Paul Thompson, Alva Claude Surber Jr. and Roy J. Popkin, Los Angeles.

### COLORADO

**National Youth Health Program.**—A statewide health project will be set up under the sponsorship of the Colorado State Board of Health as a part of a health program now being established by the National Youth Administration of Colorado for its out-of-school youth. The primary purpose will be to provide health examinations to NYA out-of-school youth on projects throughout the state, to cooperate with local agencies in arranging for necessary reparatory work and to maintain health records for the individual youths. The program is to be directed by a state medical consultant who will be employed on the administrative staff of NYA and will be compensated at the rate of \$18 a day on a one-fourth time basis. The state medical society through its public policy committee is cooperating with the NYA in the organization of the program and in the selection of the state medical consultant and a supervisor, the latter to work under the direction of the consultant.

### ILLINOIS

**Public Health Association.**—The Illinois Public Health Association was organized at Springfield on December 5 at a meeting called for that purpose by local health officers and others interested. The association is a voluntary agency, the object of which is to promote interest in public and individual health, according to the *Illinois Health Messenger*. Officers are Dr. Arlington Ailes, health officer of LaSalle, Peru and Oglesby, president; Barter K. Richardson, senior administrative officer, state department of public health, vice president, and Dr. Howard A. Orvis, health officer of Winnetka, secretary.

**The State Needs Physicians.**—The state department of public health has openings for young physicians who wish to make public health work their career. Five of these physicians are scheduled to begin a year's training at a recognized school of public health in February, all expenses to be paid by the state and federal governments. At the end of their training the physicians will be eligible to take civil service examinations for district health superintendent and other public health service positions. Persons who are accepted for the training course are required to pledge themselves to remain in public health work for three years. The maximum age limit on applicants is 35 years. The state department also has openings for nine young physicians who are to be placed as assistants to the superintendents in district health offices, with the training course being made available to them next year. Applications may be sent to the state director of health, Statehouse, Springfield.

### Chicago

**Dr. Herrick Will Give Fenger Lecture.**—Dr. James B. Herrick will deliver the fifth Christian Fenger Lecture of the Institute of Medicine of Chicago and the Chicago Pathological Society at the Palmer House, February 10. His subject will be "Christian Fenger as I Knew Him, 1885-1902: A Study in Personality."

**The Bacon Lectures.**—Prof. Henrik Dam of the Biochemical Institute, University of Copenhagen, will deliver the Charles Sumner Bacon Lectures for 1940-1941 at the University of Illinois College of Medicine. Professor Dam will speak February 12 at 1 p. m. on "Vitamin K, Its General Significance in Biochemistry," and February 13 at 4 p. m. on "Vitamin K, Its Role in Human Pathology and Its Application in Therapeutics."

**Course in Electrocardiographic Interpretation.**—A course in electrocardiographic interpretation for graduate physicians will be given at Michael Reese Hospital by Dr. Louis N. Katz, director of cardiovascular research. The class will meet each week for twelve weeks, beginning February 19. Additional information and a copy of the program may be obtained by writing to the Cardiovascular Department, Michael Reese Hospital.

**National Social Hygiene Day.**—The Illinois Social Hygiene Association will hold a special program at the Palmer House February 5 to observe National Social Hygiene Day. Dr. Irving S. Cutter, dean, Northwestern University Medical School, will be chairman at the luncheon meeting. The afternoon program will be given over to four phases of social hygiene: medical, educational, law enforcement and social protective measures.

**Psychiatric Meeting.**—The Illinois Psychiatric Society will meet at the Medical and Dental Arts Building February 6. The speakers will be: Drs. Emma Sylvestre-Pollaczek on "Clinical Examples of Child Psychotherapy"; Lloyd H. Ziegler and Merle Q. Howard, Wauwatosa, Wis., "Psychoses and Allied States Occurring Subsequent to Thyroidectomy," and Alexander R. MacLean, Rochester, Minn., "Treatment of Orthostatic Hypotension and Orthostatic Tachycardia on the 'Head-Up' Bed."

### KANSAS

**Society News.**—The Northwest Kansas Medical Society was addressed at Colby recently by Drs. Clarence R. Schmidt, Halstead, on "The Role of Hepatic Physiology in the Preoperative Preparation of Patients"; William S. Walsh, Halstead, "The Value of the Hippuric Acid Test of Liver Function in Thyroid Disease," and Charles Douglas Deeds, Denver, "Heart Failure."—Dr. Philip W. Morgan, Emporia, discussed heart disease before the Wabanssee County Medical Society in Eskridge recently.—The Wyandotte County Medical Society was addressed, December 17, in Kansas City by Drs. Louie F. Barney on "Modern Concepts of Wounds and Their Treatment" and William H. Algie, "The Clinical-Neurological Examination." Both are of Kansas City. The society was addressed, January 21, by Drs. Edgar F. DeVillbiss and Lee H. Leger, Kansas City, on "Use of Metrazol in Treatment of Mental Diseases" and "Headaches and Head Pain," respectively.—Dr. Henry H. Turner, Oklahoma City, addressed the Sedgwick County Medical Society, Wichita, January 21, on "Present Status of Endocrinology in General Practice."—Dr. Arthur D. Gray addressed the Shawnee County Medical Society in Topeka, January 6, on "Sulfanilamide and Its Derivatives in the Treatment of Genito-Urinary Infections."

### KENTUCKY

**Personal.**—Dr. William J. Gerding, Newport, was honored with a testimonial dinner December 12 by his colleagues on the staff of St. Elizabeth's Hospital, Covington, and representatives of the hospital's school of nursing. The dinner marked Dr. Gerding's completion of twenty-five years as instructor in materia medica in the school of nursing and thirty-two years on the staff of the hospital. Dr. Philip H. Dorger, Covington, was toastmaster.

**Society News.**—Dr. James M. Kinsman, Louisville, addressed the Bourbon County Medical Society, Paris, December 19, on "The Present Status of Sulfanilamide, Sulfapyridine and Sulfathiazole."—Speakers at a meeting of the Muldraugh Medical Society December 12 were Drs. Harry S. Andrews, Louisville, on "Pneumonia in Children"; Ruel T. Routt, Sonora, "Home versus Hospital Treatment of Pneumonia," and Samuel A. Overstreet, Louisville, "Chemotherapy in Pneumonia."

**Changes in State Hospital Administration.**—Dr. Addie M. Lyon, superintendent of the Western State Hospital, Hopkinsville, has been appointed director of state hospitals and mental hygiene to succeed Dr. Joseph G. Wilson, Frankfort, resigned. The appointment was made by W. A. Frost, recently appointed state commissioner of welfare. Dr. William R. Summers, superintendent of the Central State Hospital, Lakeland, will succeed Dr. Lyon at Hopkinsville and Dr. Isham Kimball,

manager of the Veterans Administration Facility at Gulfport, Miss., will come to the Lakeland hospital. Dr. Lyon was recommended for the state directorship by an advisory committee of the Kentucky State Medical Association.

### MICHIGAN

**The Beaumont Lectures.**—Dr. Armand Quick, associate professor of pharmacology, Marquette University School of Medicine, Milwaukee, will deliver the annual Beaumont lectures of the Wayne County Medical Society, February 3 and 10. His subject will be "The Coagulation of the Blood and Its Relation to Hemorrhagic Diseases."

### MISSOURI

**Society News.**—Dr. Owen S. Gibbs, Memphis, Tenn., will discuss "Drug Poisoning and Its Management" before the Kansas City Academy of Medicine, February 21.—Dr. Carl H. B. Schutz, Kansas City, discussed "Anatomical Routes of Infection To and From the Urinary Tract" before the Kansas City Urological Society, January 9.—Dr. Edward Lee Dorsett, St. Louis, discussed "Why Is It Necessary to Reoperate in Certain Gynecological Cases?" before the Kansas City Society of Obstetrics and Gynecology, January 9.

**Dr. Crossen Honored.**—Dr. Harry Sturgeon Crossen, since 1935 professor emeritus in gynecology at Washington University School of Medicine, St. Louis, was guest of honor at a dinner given at the university on November 23. Dr. George Gray Ward, New York, the guest speaker, discussed "The Advances in Gynecology in the Past Fifty Years." On the same day the St. Louis Obstetrical and Gynecological Society gave a luncheon to Dr. Ward, when he spoke on "Carcinoma of the Cervical Stump Following Hysterectomy."

**Professor Schmidt Goes to Massachusetts.**—Francis O. Schmidt, Ph.D., Rebstock professor of zoology, Washington University, St. Louis, has been appointed professor of biology in charge of the program in biologic engineering at the Massachusetts Institute of Technology, according to the *New York Times*. Dr. Schmidt is expected to advance the close cooperation between the institute's department of biology and public health and the departments of physics, chemistry and electrical engineering. This broad program of education and research in biologic engineering is going forward under a grant of \$200,000 from the Rockefeller Foundation. Dr. Schmidt took his doctor's degree at Washington in 1927 and after some work abroad returned to his alma mater in 1929 as assistant professor of zoology.

### MONTANA

**Dr. Cox Receives Theobald Smith Award.**—The 1940 Theobald Smith award in medical science was presented to Herald R. Cox, Sc.D., principal bacteriologist of the U. S. Public Health Service, Hamilton, during the recent meeting of the American Association for the Advancement of Science in Philadelphia. Dr. Cox, who is stationed at the Rocky Mountain Laboratory of the public health service, received the award "for his outstanding research in the rickettsial diseases, resulting in the development of a new technic for the preparation of protective vaccines against Rocky Mountain spotted fever and typhus fever." In 1931 Dr. Cox graduated at Johns Hopkins University, Baltimore, where he served for a time as instructor in immunology. He also served as assistant in bacteriology and pathology at the Rockefeller Institute for Medical Research, New York. He was appointed associate bacteriologist in the public health service in 1936 and promoted to principal bacteriologist in 1940. The Theobald Smith Award was established in 1935 by Eli Lilly and Company, to be bestowed on an investigator under 35 years of age for "demonstrated research in the field of medical sciences, taking into consideration independence of thought and originality." The award consists of a bronze medal and \$1,000.

### NEW JERSEY

**Hospital Changes.**—Dr. Herbert McC. Wortman, assistant superintendent of Mountainside Hospital, Montclair, has been appointed superintendent to succeed Dr. Charles H. Young, who has been appointed administrator of Jefferson Hospital, Birmingham, Ala.—Dr. Thomas Howell, superintendent of Overlook Hospital, Summit, has resigned, it is reported.

**Society News.**—Dr. Lewis D. Stevenson, New York, addressed the Hudson County Medical Society, Jersey City, January 7, on "Recent Advances in the Diagnosis and Treatment of Diseases of the Nervous System."—A symposium on diseases of the thyroid gland was presented before the

Morris County Medical Society, Morris Plains, January 16, by Drs. Frank H. Pinckney, George H. Lathrop and George J. Young, Morristown.—Drs. Harvey B. Matthews, Brooklyn, and Arthur W. Bingham, East Orange, addressed the Gloucester County Medical Society, Woodbury, January 16, on "Management of Prolonged Labor" and "Lessons to Be Learned from a Study of Maternal Mortality" respectively.

**Prosecutions by State Board.**—The state board of medical examiners recently reported the following cases of illegal practice and the results of prosecutions, among others:

Wellington A. Allen, Plainfield, who posed as a physician, pleaded guilty and was sentenced to ten days in jail.

Michael Nogradi and Philip Manna, unlicensed chiropractors of New Brunswick, paid penalties for practicing without a license.

Andrew V. Pulcrano, Lakewood, paid the penalty for practicing without a license.

Frank Crawford, Williamstown, a registered pharmacist, paid a penalty for practicing medicine without a license.

Florence Goldstein, a herbalist of Passaic, paid the penalty for practicing without a license.

Francis X. Halligan, Toms River, a registered pharmacist, paid the penalty for practicing medicine without a license.

Harold Singer, Jersey City, a licensed chiropodist who exceeded his license by giving electrical treatments and manipulations, paid a penalty for practicing without a license.

**Medical Preparedness in Case of Disaster.**—The medical preparedness division of the mayor's security committee of Elizabeth has outlined a plan for medical action in the event of a disaster. Buildings near each hospital have been selected to be used as reception centers if hospitals overflow their capacities. In case of a greater emergency, seven churches will be used as overflow stations. The medical setup will be under the supervision of a "medical director," who will coordinate work of the physicians with the police, the Red Cross, the hospitals and the transportation committee. The director will appoint teams to man the reception centers while other physicians go direct to the scene of the emergency. Detailed plans have been worked out for emergency treatment and transfer of injured to hospitals and reception centers. Definite arrangements must be made with the Red Cross to provide adequate equipment for the emergency teams, a trained civilian corps of ambulance drivers, stretcher bearers and clerks, nurses and a central joint headquarters for the Red Cross officer and the medical director. Dr. Rocco M. Nittoli, Elizabeth, is chairman of the medical preparedness committee.

### NEW YORK

**Expanded Case Finding Tuberculosis Program.**—A special coordinating committee has been appointed by Dr. Edward S. Godfrey Jr., state health commissioner, to launch an expanded case finding and control program in an effort to eradicate tuberculosis in New York State outside of New York City. The committee includes Drs. Robert E. Plunkett and Vivian A. Van Volkenburgh and Miss Marion Sheahan of the state health department, Albany; Dr. William J. Tiffany, Albany, state commissioner of mental hygiene; Dr. Peter Irving, New York, secretary of the Medical Society of the State of New York; Dr. Donald B. Armstrong, New York, third vice president, Metropolitan Life Insurance Company; David C. Adie, state commissioner of social welfare; Homer Folks, LL.D., secretary; George J. Nelbach, executive secretary, and Robert W. Osborn, assistant executive secretary of the State Charities Aid Association, New York. The committee's efforts will be directed toward examination of contacts, examination of persons with typical symptoms, case finding among susceptible groups and more effective utilization of hospitalization to break the chain of infection, it was reported.

### New York City

**Academy to Increase Endowment.**—The New York Academy of Medicine has begun a five year program to raise funds to carry on its activities, Dr. Malcolm Goodridge announced on the occasion of his inaugural address beginning his second term as president. The academy needs \$500,000 for changes in the library and for support of the annual budget. It is hoped to increase the endowment fund by \$1,250,000 in the five years under the leadership of a committee with Dr. Harold R. Mixsell as chairman. Dr. Goodridge pointed out that a deficit of \$18,000 for the year ended Dec. 31, 1939 had been met by a gift from Mr. Bernard M. Baruch.

**Association of Dermatophiliologists.**—Formation of the Association of Dermatophiliologists of Greater New York is announced. Officers are Drs. Howard Fox, president; George Miller MacKee, president-elect, and Maurice J. Costello, secretary. Purposes of the society were announced as follows: appointment of a dermatophiliologist to the medical

advisory boards in the national defense program; adjustment of difficulties in connection with workmen's compensation; efforts to seek cooperation of hospital officers and physicians in charge of outpatient departments in directing compensable dermatoses to private physicians; elimination of violations of the medical practice act by lay practitioners and corporations in treatment of cutaneous diseases, and clarification of the status of the dermatosyphilologists under the various prepayment medical service plans.

### OHIO

**Ophthalmologist Leaves Funds for Research.**—The residuary estate of the late Dr. Walter H. Snyder, Toledo, which is valued at \$350,000, has been released by court action for the establishment of the Snyder Ophthalmic Foundation to provide funds for research in diseases of the eye. By trust agreements made several years ago Dr. Snyder and his wife, who died in 1937, placed the bulk of their property in trust and directed that on their deaths the funds should be used for research in ophthalmology and other charitable purposes. Following Dr. Snyder's death in 1938 the will was contested by relatives. The research funds are to be administered by five directors, including Drs. Conrad Berens and John H. Dunnington, New York.

**Society News.**—Dr. Frank Dennette Adams, Boston, will address the Mahoning County Medical Society, Youngstown, February 18, on "Some Clinical Considerations of Chronic Headache."—Speakers at the meeting of the Summit County Medical Society, Akron, January 7, included Drs. Elgie R. Shaffer, Columbus, "The Vaccine or Serum Treatment of Whooping Cough"; Paul R. Adams, Akron, "The Relationship of Coronary Disease of the Heart to Heart Disease in General," and William McK. Johnston, Akron, "Surgery of the Thyroid."—Dr. Warfield M. Firor, Baltimore, addressed the Academy of Medicine of Cincinnati, January 7, on "Use of Sulfanilylguanidine in Surgery."—Dr. Clarence O. Sappington, Chicago, addressed the Montgomery County Medical Society, Dayton, January 17, on "Modern Appraisal of Industrial Medicine."

### PENNSYLVANIA

**Biologist Dies.**—David Hilt Tennent, Ph.D., research professor of biology at Bryn Mawr College, Bryn Mawr, died January 14, aged 67. Dr. Tennent had been associated with the college since 1904 and had conducted investigations in many parts of the world. He had served as president of the American Society of Zoologists and the American Society of Naturalists.

### Pittsburgh

**Symposium on Public Health.**—The Allegheny County Medical Society presented a symposium on public health and preventive medicine at its meeting, January 21. Dr. John J. Shaw, state secretary of health, made an address of welcome, and the speakers were Drs. Huntington Williams, Baltimore, on "New Aspects of Municipal Health Administration"; John M. Campbell Jr., Harrisburg, "Recent Advances in Control of Communicable Diseases"; Chauncey L. Palmer, Pittsburgh, "The Physician's Interpretation of Public Health Laws in Allegheny County and Pennsylvania," and Charles Howard Marcy, Pittsburgh, "The Problem of Tuberculosis Control in Pittsburgh and Allegheny County."

### RHODE ISLAND

**Society News.**—Drs. John B. Sears, Boston, and Seebert J. Goldowsky addressed the Providence Medical Association, January 6, on "Phlebitis, Ulcers, the Thromboses" and "Modern Treatment of Varicose Veins" respectively.—Dr. Henry S. Joyce, Providence, was recently elected president of the Hospital Association of Rhode Island and Dr. Harmon P. B. Jordan, Providence, vice president.

### WEST VIRGINIA

**Conference of County Society Officers.**—The annual conference of county medical society secretaries and presidents of the West Virginia State Medical Association was held in Charleston, January 18. The speakers were:

Dr. Robert K. Buford, Charleston, president of the state association, Our 1941 Medical Program in West Virginia.  
Major Luther R. Lambert, Fairmont, state medical officer for selective service, The Doctor and Preparedness.  
Dr. Carl M. Peterson, director, Council on Industrial Health, American Medical Association, Chicago, Industry and Health.  
Dr. Ward Wythe, Mullens, Medical Legislation.  
Mr. William J. Burns, executive secretary, Michigan State Medical Society, Lansing, Michigan's Voluntary Medical Insurance Plan.  
Dr. Russel Kessel, Charleston, Medical Organization and Public Affairs.

### WISCONSIN

**Nursing Services in Industry.**—The state board of health and the industrial nurses of Wisconsin are sponsoring a symposium on industrial public health nursing services, which will be held at the Hotel Wisconsin, Milwaukee, February 20-22. Dr. Paul A. Brehm, Madison, supervisor of the industrial hygiene unit of the state board of health, is general chairman of the program, which includes the following speakers:

Dr. Stanley J. Seeger, Milwaukee, chairman, Council on Industrial Health, American Medical Association, Relationship of the Nurse in Industry to the Physician.  
J. J. Bloomfield, U. S. Public Health Service, Washington, D. C., Responsibility of the Nursing Profession in Industrial Hygiene.  
Mr. Harry Guilbert, safety director, the Pullman Company, Chicago, The National Defense Program and the Industrial Worker.  
Dr. Norbert Enzer, Milwaukee, Relationship of Cardiovascular Diseases to Accidents.  
Dr. Richard D. Mudd, Saginaw, Mich., and Mr. W. G. Hazard, Owens-Illinois Glass Company, Toledo, Absenteeism in Industry.

There will be two panel discussions, one on "After the Injury—What?"; the other, "Community Resources as They Concern the Nurse in Industry."

**Society News.**—The Hon. Alexander P. Wiley, U. S. Senator from Wisconsin, addressed the Medical Society of Milwaukee County, December 12, on "Changing Social Conditions and Their Effect on the Future of Medicine"; the incoming president, Dr. Timothy J. Howard, Milwaukee, gave his official address.—Dr. Robert L. Bennett Jr., Madison, addressed the Brown-Kewaunee-Door County Medical Society, Green Bay, December 16, on physical therapy in rheumatoid arthritis.—Drs. Charles F. Burke and Herbert W. Virgin Jr., Madison, addressed the Dane County Medical Society, Madison, December 10, on "Treatment of Congestive Heart Failure" and "Experimental Replacement of Long Bone Shafts with Vitallium" respectively.—Dr. John A. Schindler, Monroe, addressed a joint meeting of the Green and Lafayette county medical societies in Monroe, December 13, on "Treatment of Alcoholic Cirrhosis of the Liver."—Dr. Elmer L. Sevringhaus, Madison, addressed the La Crosse County Medical Society, La Crosse, December 17, on "Menstrual Irregularities and Sterility."—Dr. Robert E. Burns, Madison, discussed "Trauma of the Back" at a meeting of the Rock County Medical Society, Janesville, December 17.—Dr. Milton C. Borman, Milwaukee, addressed the Winnebago County Medical Society, Oshkosh, January 2, on "Practical Handling of Rheumatism."—Dr. Andrew C. Ivy, Chicago, addressed the University of Wisconsin Medical Society, Madison, January 17, on "Bile Acid Metabolism and Therapy."

### GENERAL

**The Influenza Outbreak.**—The U. S. Public Health Service reported January 23 that, up to January 18, 120,006 cases of influenza had been reported in the United States, a rise of 30,178 in one week. It was reported January 11 that 18,000 school children in Boston were ill with a mild form of the disease. Classes had been suspended in Salem, Haverhill and Gardner, Mass., and in Augusta, Me. One lumber camp deep in the Maine woods reported nearly a third of the lumberjacks had influenza and colleges in Maine were said to have suspended social activities and sports events. Outbreaks were also reported in Georgia, Louisiana, Arkansas and Tennessee. In Chicago, the health commissioner reported that 80 cases of influenza had been reported this year up to January 21 as compared with 47 for the previous year. In New York 84 cases were reported January 23 for the preceding twenty-four hours, a decline from 140 reported two days before. The health department considered that the prevalence had not reached the proportions of an epidemic.

**"Medical Pilots."**—The group known as "Medical Pilots" has printed its by-laws, which state that the organization is to be devoted to the mutual enjoyment and advancement of aviation among doctors of medicine. It is not a military organization and, when the present shortage of airplanes is ended, the organization hopes to make group flights. At present it holds monthly dinners to which noted aviation personalities in commercial and military circles are invited. The emblem, "Wings on the Caduceus," shall be worn only by active pilot members or by members who have been active pilots, the by-laws provide. The associate and honorary members wear no insignia. The Charter Hangar may grant the use of the name "Medical Pilots" to other organizations of medical pilots outside the county of Los Angeles by a majority vote of the members, provided the use of the name and insignia are granted only to organizations which adopt the principles of the Charter Hangar as their own. All members of "Medical

Pilots" shall conform to the principles of medical ethics of the American Medical Association and to the rules and regulations of the U. S. Department of Commerce, Bureau of Air Commerce. The secretary is Dr. Colby Hall, 1136 West Sixth Street, Los Angeles, Calif.

**Grants Available from the Plotz Foundation.**—The Ella Sachs Plotz Foundation announces that applications for grants to be held during the year 1941-1942 must be in the hands of the executive committee by April. These grants are usually less than \$500. Researches will be favored that are directed toward the solution of problems in medicine and surgery or in branches of science bearing on medicine and surgery. The grants may be used for purchase of apparatus and supplies needed for special investigations and for unusual expenses but not for materials that are ordinarily a part of laboratory equipment. There are no formal application blanks, but letters must state definitely the qualifications of the investigator, an accurate description of the research, the size of the grant requested and the specific use of the money. Applicants should state whether they have approached other foundations for financial assistance. Letters of recommendation from the directors of the departments in which the work is to be done are desirable. The foundation reports that in the past year it made twenty-three grants. Eighty-one applications were received, fifty-one from the United States and the others from fifteen countries. Of the grants one went to China, one to Argentina and the remainder to investigators in the United States. In the seventeen years of its existence the foundation has made three hundred and ninety-four grants.

## Government Services

### Positions for Physiotherapy Aides

The U. S. Civil Service Commission announces open competitive examinations for the positions of physical therapy aide, paying \$1,800 a year, and for junior physical therapy aide, paying \$1,620 a year. Applications must be on file with the commission not later than February 17 and 20, the later date being for applicants living west of Colorado. Information and application forms may be obtained from the secretary of the board of civil service examiners at any first or second class post office or from the commission at Washington, D. C.

### Meeting of Advisory Cancer Council

The National Advisory Cancer Council held a session at the new National Cancer Institute laboratory at Bethesda, Md., January 6. Dr. Ludvig Hektoen, executive director of the council, reported that during the last three years grants-in-aid totaling \$271,277.50 have been made. Applications for grants which would have totaled \$1,995,635.25 were considered, it was said. Of the amount granted \$129,085 was for fundamental cancer research, \$49,652.50 for clinical cancer research and \$92,570 for experimental work in connection with the cyclotron. Carl Voegtlin, Ph.D., chief of the National Cancer Institute, reported that the institute now has a staff of thirty-eight scientists and fifty technicians trained for specific investigations. Dr. Cornelius P. Rhoads, director of the Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York, and Edward A. Doisy, Ph.D., professor and director of the department of biochemistry, St. Louis University School of Medicine, were recently named as members of the advisory council and Dr. Hektoen was reappointed executive director.

### Public Health Assistants Needed

The U. S. Civil Service Commission announces examinations to fill the positions of psychiatric nurse, guard-attendant and medical technical assistant in the division of mental hygiene of the U. S. Public Health Service. Applicants for the position of psychiatric nurse, which pays \$3,200 a year, must be registered graduate nurses with experience in a hospital for mental patients. They will not be required to take a written test. Applicants for the medical guard attendant positions must be registered graduate nurses, with experience as attendant at federal penal or correctional institutions or service in the army or navy medical corps. The salary is \$1,620 a year. For medical technical assistant positions, applicants must meet the requirements for the guard attendants and in addition must have had one year of training or experience in either clinical

laboratory technic, pharmacy or roentgen ray laboratory technic. Applications must be filed at the Washington office of the civil service commission not later than February 17 and 20, the later date being for applications sent from Colorado and states westward. Information may be obtained from the Secretary, U. S. Board of Civil Service Examiners, at any first or second class post office, or from the commission at Washington, D. C.

### Advisory Council on Mental Diseases

The Advisory Council on Nervous and Mental Diseases, appointed by Dr. Thomas Parran, surgeon general, U. S. Public Health Service, Washington, met December 16 in Washington. Establishment of a national institute for research on these diseases, similar to the National Institute of Health and the National Cancer Institute, was proposed. Grants-in-aid to other institutions were also suggested as a means of furthering research. Members of the advisory council are:

Dr. Edward A. Strecker, professor of psychiatry, University of Pennsylvania School of Medicine, Philadelphia.

Dr. Nolan D. C. Lewis, medical director, New York State Psychiatric Institute and Hospital, New York.

Dr. Lloyd H. Ziegler, associate medical director, Milwaukee Sanitarium, Wauwatosa, Wis.

Dr. Abraham Myerson, clinical professor of psychiatry, Harvard Medical School, Boston.

Dr. Arthur H. Ruggles, secretary, American Psychiatric Association, Providence, R. I.

Dr. Henry W. Woltman, consultant on neurology, Mayo Clinic, Rochester, Minn.

Dr. Robert Findlay Gayle Jr., professor of neuropsychiatry, Medical College of Virginia, Richmond.

Dr. Parran, ex officio chairman of the council, presided at the meeting and Drs. Lawrence Kolb, assistant surgeon general in charge of the division of mental hygiene, U. S. Public Health Service, and Winfred Overholser, superintendent of St. Elizabeths Hospital, took part in the discussions.

### Prohibit Solicitation by Lawyers in Government Hospitals

According to an announcement of the Surgeon General of the United States Public Health Service (Federal Register 5:5220 [Dec. 21] 1940) the regulations for the government of the U. S. Public Health Service have recently been amended. This amendment prohibits the solicitation in hospitals of the U. S. Public Health Service of legal business or of a retainer or agreement authorizing an attorney to perform or render legal services. It is made the duty of the medical officer in charge, on learning of any such solicitation, to make an appropriate investigation and, if satisfied that such has occurred or is occurring, within ten days submit a detailed report to the surgeon general for appropriate action. All persons in the employ of or attached to any hospital of the U. S. Public Health Service and all patients confined therein are forbidden to communicate, directly or indirectly, with any attorney, or any person acting in behalf of such attorney, for the purpose of aiding, assisting or abetting such solicitation. However, a patient is not to be prevented from communicating with an attorney of his choice on his own behalf. No person shall knowingly be permitted to enter such a hospital for the purpose of negotiating a settlement or obtaining a general release or a statement, written or oral, from a patient within fifteen days after confinement, with reference to any personal injuries for which such patient was confined therein, unless prior to the procuring of such release or statement the injured party has signified to the medical officer in charge his willingness that such be given. All persons in the employ of or attached to any hospital of the U. S. Public Health Service and all patients confined therein are also forbidden to communicate, directly or indirectly, with any one attempting to procure such a settlement, release or statement. It is provided, however, that these prohibitions shall not apply to any release or statement obtained by or on behalf of the attorney of the person so confined and shall not prevent the medical officer in charge from giving information essential to the negotiation of a settlement. Any employee of the U. S. Public Health Service who violates any provision of this amendment to the regulations shall be immediately relieved from duty and be subjected to such further disciplinary action as is provided in the regulations. Furthermore, any patient of the U. S. Public Health Service who violates any of these provisions shall be subject to discharge for disciplinary reasons in accordance with the procedure provided by the regulations.

## Foreign Letters

### SWITZERLAND

(From Our Regular Correspondent)

Dec. 17, 1940.

#### Bombs Which Fell in Geneva

Dr. Jentzer, professor of surgery, before the medical society of Geneva, analyzed the nature of the lesions caused by the bombs that fell in the city last June. About a dozen of the injured were brought to the surgical clinic of the university. In 7 cases there were slight dotlike wounds caused by metal or stones. Several were wounded while they were in bed. One woman's breast was torn away while on a balcony; in another case the subscapular artery was severed. Two deaths occurred. In 1 case there was only a superficial wound in the thorax. At necropsy, however, two ribs were found pulverized and the powder in the lungs. In the other case a lesion occurred in the left gluteal area and the rectum. The entrance wound was small, but there was extensive internal damage and rapid infection.

#### The International Committee of the Red Cross

Several representatives of the International Committee of the Red Cross, all Swiss citizens, were active in war-torn sections of Europe, Asia and Africa. Dr. Roland Marti visited various Belgian, British, French and Polish prison camps in Germany. M. R. Haccius flew to England to visit German war prisoners and interned civilians and to pave the way for a greater cooperation of the International Red Cross with Great Britain. Mr. Collart inspected camps of interned German civilians in Syria; Georges Vaucher visited interned Italian civilians in Egypt; Dr. Marcel Junod, in the occupied section of France, sought the cooperation of military authorities for improving the conditions of interned war prisoners, especially by allowing prisoners to correspond with their relatives and by allowing visits of representatives of the International Red Cross. He visited several depots in which French prisoners were temporarily housed and a hospital in the northern part of France in which British and French wounded were cared for. He discussed plans with Prof. Pasteur Vallery Radot, the new president of the French Red Cross, for aid to war prisoners and in Paris met the director of the national information bureau for war prisoners.

#### Physiology of Digestion in Nurslings

Dr. E. Freudenberg, professor of pediatrics in Basel, spoke before the medical society of that city on the subject of the physiologic factors in the digestion of nurslings. His observations showed (1) that the mortality rate of children is highest at the nursling age and lowest between the years of 10 and 15 years, (2) that digestive and nutritional disturbances formerly constituted a principal cause of mortality in the early stage and that (3) nursling mortality is significantly affected by the use of cow's milk. Freudenberg found that mother's milk remains only a short time in the infant's stomach and that the digestion is stimulated already by a small amount of gastric juice secretion. Cow's milk, on the other hand, requires a larger quantity of gastric juice. The digestion of the albumin contained in mother's milk proceeds with extraordinary economy in time and acidity. A low acidity in the stomachs of nurslings also accompanies the splitting up of fats when mother's milk is employed, because mother's milk contains a lipase not found in cow's milk. By means of the jejunal probe, Freudenberg was able to study fermentation in the small intestine and confirmed his earlier observations that mother's milk is better for the nursling than

cow's milk. There is a more rapid decomposition of mother's milk in the intestine. The lactose of mother's milk produces in the intestinal tract of the infant a flora different from that of cow's milk. The breast-fed infant thus needs to expend digestively and nutritionally less energy to accomplish the same ends as the child nourished on cow's milk. This economy in nutritional energy enables breast-fed children to endure intestinal disturbances better. The greater demand made on the digestive apparatus of artificially fed infants entails greater disturbances of the digestion and hence a higher mortality. Numerous detailed investigations have failed to create a standardized form of artificial nutrition.

#### A Swiss Ambulance Unit in the Finnish War

Dr. Robert Nicole, assistant physician in the surgical division of the university clinic in Basel and director of the Swiss ambulance unit, made a report to the medical society of Basel on the experiences of the medical expedition. The ambulance unit had been sent on its mission of mercy at the request of the Finnish Republic with the approval of the Federal Council of the Swiss Republic. It consisted of ten physicians, nine nurses and two attendants. It had to be completed on short notice and was ready in a week. The physicians were all native German Swiss. Only surgeons were selected who had been specially trained for war surgery. The difficulties of transportation were enhanced by the fact that a circuitous route had to be adopted by way of Rotterdam to Bergen, Norway, then from Stockholm via Haparanda to Helsingfors, a route of 3,200 kilometers. The equipment, consisting of instruments, medicaments and bandage material, was planned for two months and 500 patients. The ambulance unit carried a complete hospital equipment including x-ray apparatus, sterilization trucks patterned after the Swiss army sterilizers and so on. The complete cost of equipping this medical service amounted to more than 200,000 Swiss francs (\$46,430). After the medical mission arrived in Finland, its field of operation was determined in consultation with the head of the Finnish sanitary division and the director of the Finnish Red Cross. Military events made it impossible to carry out the original plan of maintaining the ambulance unit as an independent Swiss unit. Its forces had to be divided. Some were able to give some assistance at the front, others were assigned to different hospitals and military medical stations. Most of the wounded suffered from war lesions five days old. Because of political developments, medical aid at the front could not be practiced for more than a few days.

The kinds of lesions encountered were, generally, similar in their incidence to those of the World War. Maxillary wounds did not show an increase. Among 6,000 wounded there were fifty-six maxillary lesions. Grave head and body wounds were relatively infrequent. Infection was found to set in on the third day, even in small lesions. However, its virulence was not as intense as was observed in traumas due to traffic accidents in Basel. Therapeutic procedure depended not so much on the size of the wound as on its origin. In lesions due to shell and bomb fragments excision was recommended, in lesions due to small arms conservative treatment was advised. Primary suture of war lesions was found to be a mistake because of the infection which regularly occurred. Immobilization was most effective; the use of an ointment of cod liver oil was also helpful. Amputation needs to be done far less than was done formerly. Septic hemorrhages in erosion processes were frequent and were extremely dangerous. Empyema in the joints was common. Wounded who were operated on in the first twenty-four hours often died of shock rather than of their wound. However, mortality from this cause was greatly diminished by means of intravenous narcosis. Few cases of tetanus occurred, as the troops had been prophylactically inoculated. Gas gangrene was

observed only twice. Splinters need not necessarily be removed. In many cases removal was advised against because of subsequent infection.

### Endemic Goiter

Dr. J. Eugster of Zurich, who has long studied the geographic significance of goiter, discussed the subject before the medical society of Basel. Goiter is endemic in the canton of Aargau. Confirmations are based on twenty-five years of observation. Strangely, goiter affects diversely not only certain portions of the same canton but likewise the same villages and even the same houses. Persons living in certain houses were all affected with goiter, while all those who had lived during the course of years in other houses were all free from goiters. Systematic investigation disclosed even more refined differences. In the examination of one thousand and twenty-four persons of one village it was found that 72 and 79 per cent respectively of those who lived on the first floor had goiter, whereas only 58 per cent of those living on the second floor were so affected. In the case of one thousand four hundred persons who had migrated from a district free from goiter, it was found that the next generation showed goiter in proportion to the goiter incidence of the district into which they moved, whether minimal, average or pronounced. In a family which had moved away in 1893 from a district free from goiter to one with an endemic record, it was found that all children born in that region had acquired goiter whereas one child who had not been born there remained free from the disorder. When the same family moved back to its former village, the children of the second generation born there were free from the disease, though their parents had goiter. It is inferred that the fetal period determines the presence or absence of goiter. In large families, subsequently born children showed goiter more plainly. Likewise in persons born in certain years (e. g. 1903 and 1906) the goiter incidence was higher than in other years. Eugster thinks that climatic factors are involved, since trees were observed in both of these years to have developed more vigorous annual rings. Eugster also examined five hundred and eleven pairs of twins. He found that of a pair of twin sisters moving from a region with endemic goiter into one free from it, the one living on the first floor developed goiter, the other living on the second floor did not. In other cases involving twins, one sister moved into an endemic district and contracted goiter; the other moving into one free from goiter remained unaffected. Uniovularity or biovularity did not make a difference. Eugster believes that a number of individual factors are involved. For example, persons living in houses built on a rock foundation remained free from goiter, whereas those living in houses built on rock material originally derived from the same rock basis have for decades been affected with goiter. Goiter is not hereditary. Spontaneous cures, in which no medication is employed, occur frequently.

### Swiss Aid for France

The Swiss Society for War Harassed Children, working in cooperation with American Quakers, has displayed great activity in France. Recently a canteen was opened in the town of Constantine to serve milk to the children of refugees. Four tons of powdered milk was served to children of eight hundred Belgian war refugees sheltered in barracks at Toulouse. Several other milk distribution centers have been established, and additional tons of condensed and dried milk have been supplied. Children bring their own bread.

### Personals

Dr. F. R. Nager, professor of otorhinolaryngology in Zurich and dean of the medical faculty, delivered the Semon Lecture at the University of London. This is the first time that a Swiss was invited.

Dr. Louis Michaud, professor of internal medicine at the University of Lausanne, celebrated his sixtieth birthday. The

*Schweizerische medizinische Wochenschrift* honored the occasion by a festive edition embracing three increased current issues. The *Revue médicale de la Suisse romande* likewise published an issue in his honor. Michaud has been connected with the University of Lausanne as professor and director of the medical clinic since 1913 and has specialized in diseases of the kidneys.

Prof. C. Dorno, climatologist, celebrated his seventy-fifth birthday. In 1907 he created the physicometeorologic observatory at Davos for the investigation of the therapeutic effects of high mountain altitudes. His investigations made him the founder of radiation climatology and medical climatology. The institute founded by him is now maintained at public expense.

Dr. A. Gigon, professor of internal medicine and editor of the *Schweizerische medizinische Wochenschrift*, was elected dean of the faculty of medicine of Basel.

### Deaths

Dr. Max Cloëtta, for many years professor of pharmacology and director of the pharmacologic institute of the University of Zurich, died June 23, 1940, at the age of 72 years. He was a native of Zurich, where he began his academic career in 1898 and advanced rapidly to a professoriate in 1901. Though invited to Göttingen and Munich, he remained in Zurich until 1935, when he retired for reasons of health. With Cloëtta Switzerland's leading pharmacologist passed away, a scholar of international reputation and a man of noble personality.

Dr. Max Askanazy, professor emeritus of pathologic anatomy in the faculty of Geneva, died Oct. 23, 1940, at the age of 75 years. Askanazy was born in East Prussia and began his academic career at the university of Königsberg, joined the faculty of medicine of Geneva in 1905 and served there until his retirement in 1939. His special fields of research were diseases of the blood, malignant tumors and the pathology of bones. He was an excellent teacher. He founded the international society for geographic pathology. In 1935 he was made an honorary citizen of Geneva.

Dr. Eugen Enderlen, for a number of years professor of surgery in Basel, died at the age of 78 in Stuttgart. In 1905 he was called to Würzburg and in 1918 accepted a full professorship to Heidelberg. He specialized in abdominal surgery and blood transfusion.

## Marriages

LOUIS FLEXNER CLEARY, Lexington, Ky., to Miss Cora Leach Kielkopf near Lynchburg, Va., Oct. 3, 1940.

CLAUDE M. MEARS, Lewistown, Mont., to Miss Virginia Maye Cartier at Spokane, Wash., Oct. 8, 1940.

DAVID CROCKER, Fitchburg, Mass., to Miss Mary Bliss Reed of New Haven, Conn., Sept. 14, 1940.

DONALD W. MCCORMICK, Madison, Wis., to Miss Margaret Ann King of Shawano, Sept. 7, 1940.

WILLIAM WIAIT DAVIS, Parkersburg, W. Va., to Miss Mary Lydenberg in Baltimore, Oct. 5, 1940.

ARTHUR CALDWELL DUNLAP to Miss Emily Jeannette Mandile, both of Paris, Tenn., Oct. 5, 1940.

ALBERT S. EPPERSON, Cameron, Texas, to Mrs. Jessie Burton Watson of Houston, Oct. 10, 1940.

WILLIAM K. ANDERSON, Saginaw, Mich., to Miss Ethel A. Scott of Bad Axe, Oct. 12, 1940.

RICHARD F. SLAUGHTER, Augusta, Ga., to Miss Jane Caruthers of Winder, Oct. 10, 1940.

JOHN MALCOLM ASTE to Mrs. Jane Boyce Crump, both of Memphis, Tenn., Oct. 3, 1940.

ALLAN L. COHN, Minden, La., to Miss Ruby Mae Foster at Farmerville, Oct. 8, 1940.

CARL W. KUMPE, Covington, Ky., to Miss Ruth Lang of Cincinnati, Sept. 14, 1940.

WILLIAM A. McMAHON to Miss Barbara Brygger, both of Seattle, Oct. 5, 1940.



## Deaths

**Calvin Richards Hannah** \* Dallas, Texas; Illinois Medical College, Chicago, 1904; vice president of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons and member of the Central Association of Obstetricians and Gynecologists; fellow of the American College of Surgeons; past president of the State Medical Association of Texas and the Texas Association of Obstetricians and Gynecologists; professor of obstetrics and head of the department, Baylor University College of Medicine; on the staffs of the Baylor and Parkland hospitals; aged 68; died, Dec. 16, 1940, of coronary thrombosis.

**Harry Quigg Fletcher** \* Chattanooga, Tenn.; Johns Hopkins University School of Medicine, Baltimore, 1909; member of the American Association for the Surgery of Trauma; fellow of the American College of Surgeons; past president of the Chattanooga and Hamilton County Medical Society; served during the World War; visiting surgeon on the staff of the Baroness Erlanger and Children's hospitals; aged 57; died, Dec. 7, 1940, of pulmonary embolism following coronary occlusion.

**Miffin B. Brady** \* Cincinnati; Medical College of Ohio, Cincinnati, 1890; associate professor of contagious diseases, University of Cincinnati College of Medicine; member and past president of the city board of health; formerly president of the Certified Medical Milk Commission of the Academy of Medicine; medical examiner of the Probate Court; on the staff of the Cincinnati General Hospital; aged 72; died, Dec. 8, 1940, in the Bethesda Hospital of heart disease and arteriosclerosis.

**Christian Deetjen**, Baltimore; Julius-Maximilians-Universität Medizinische Fakultät, Würzburg, Bavaria, Germany, 1890; member of the Medical and Chirurgical Faculty of Maryland; was a student of Roentgen before the discovery of the roentgen ray and was first to introduce roentgen ray methods in Baltimore; as a result of roentgen ray work lost most of his fingers and later one arm; aged 77; died, Dec. 28, 1940, of arteriosclerosis.

**Nicholas Albert Baltzell** \* Marianna, Fla.; Medical Department of Tulane University of Louisiana, New Orleans, 1902; president of the state board of health; past president of the state board of medical examiners; past president of the Florida Railway Surgeons' Association; medical director and owner of a hospital bearing his name; aged 63; died, Dec. 8, 1940, in Jacksonville.

**Ethan Allen Campbell** \* Chester, Pa.; University of Pennsylvania Department of Medicine, Philadelphia, 1905; fellow of the American College of Surgeons; served during the World War; on the staffs of the Taylor Hospital, Ridley Park, Chester Hospital and the J. Lewis Crozer Home and Hospital; aged 62; died, Dec. 4, 1940.

**John Meredith Burgin** \* Bedford, Ind.; University of Louisville (Ky.) School of Medicine, 1936; member of the Kentucky State Medical Association; was commissioned a first lieutenant in the medical corps of the United States Army in 1938; retired in 1940 for disability; aged 33; died, Nov. 17, 1940.

**Charles F. Shollenberger**, Denver; Jefferson Medical College of Philadelphia, 1885; member of the Colorado State Medical Society; at one time professor of pediatrics at the Denver and Gross Medical College; formerly on the staff of St. Anthony's Hospital; aged 82; died, Nov. 11, 1940.

**John Gerrit Huizinga** \* Holland, Mich.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1890; member of the American Academy of Ophthalmology and Otolaryngology; aged 72; died, Dec. 20, 1940, in the Lakeshore Hospital, Lake City, Fla. of a ruptured appendix.

**Joseph A. Capozzi**, New York; Columbia University College of Physicians and Surgeons, New York, 1928; member of the Medical Society of the State of New York; on the staffs of the Harlem and Columbus hospitals; aged 44; died, Dec. 6, 1940, of rheumatic heart disease.

**Frederick Joseph Cox**, Gilbertsville, N. Y.; Albany Medical College, 1892; fellow of the American College of Physicians; aged 74; died, Dec. 5, 1940, in the Flower and Fifth Avenue Hospitals, New York, of bronchopneumonia, gangrene of the left leg and arteriosclerosis.

**Thomas Mayes Hopkins**, Denver; Denver College of Medicine, 1901; member of the Colorado State Medical Society; served during the World War; aged 69; died, Nov. 19, 1940, at the Presbyterian Hospital of splenic thrombosis, myocarditis and hypostatic pneumonia.

**John Crittenden Gorsuch**, Denver; University of the City of New York Medical Department, 1892; member of the Colo-

rado State Medical Society; served during the World War; aged 77; died, Nov. 26, 1940, in the Fitzsimons General Hospital of arteriosclerosis.

**Walter L. Rose**, Woodward, Okla.; Central Medical College of St. Joseph, Mo., 1903; Ensworth Medical College, St. Joseph, 1909; member of the Oklahoma State Medical Association; aged 64; died, Nov. 13, 1940, at Halstead, Kan., of bronchiogenic carcinoma.

**David Laughlin Cowden**, Cambridge, Ohio; Ohio Medical University, Columbus, 1893; member of the Ohio State Medical Association; formerly secretary of the Guernsey County Medical Society; county health officer; aged 73; died, Dec. 6, 1940, of cerebral hemorrhage.

**Joseph Nicholson** \* Los Angeles; University of Minnesota College of Medicine and Surgery, Minneapolis, 1903; at one time health officer of Brainerd, Minn.; on the staff of the California Lutheran Hospital; aged 62; died, Nov. 5, 1940, of cerebral thrombosis.

**Samuel Thomas King**, Baldwin, N. Y.; College of Physicians and Surgeons, medical department of Columbia College, New York, 1883; for many years member of the board of health of New York; aged 83; died, Nov. 23, 1940, of myocarditis and arteriosclerosis.

**Robert Emmett Conway**, Indianapolis; Indiana University School of Medicine, Indianapolis, 1916; member of the Indiana State Medical Association; on the staffs of the City Hospital and St. Vincent's Hospital; aged 51; died, Nov. 30, 1940, of coronary occlusion.

**Albion Older Bernstein**, New York; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1939; intern at the Beth Israel Hospital; aged 28; was drowned, Nov. 23, 1940, when his car plunged into the East River.

**Milton Ellsworth Hartman**, Allentown, Pa.; Jefferson Medical College of Philadelphia, 1902; member of the Medical Society of the State of Pennsylvania; on the staff of the Allentown Hospital; aged 63; died, Nov. 28, 1940, of coronary disease.

**Edward Joseph Dailey** \* Somerville, Mass.; Tufts College Medical School, Boston, 1904; served during the World War; aged 61; died, Dec. 10, 1940, in the Massachusetts General Hospital, Baker Memorial, Boston, of injuries received in a fall.

**Edmond John Melville**, St. Petersburg, Fla.; Queen's University Faculty of Medicine, Kingston, Ont., Canada, 1892; member of the Florida Medical Association; served during the World War; aged 72; died, Nov. 28, 1940, of heart disease.

**Harold Wilson**, Conneaut, Ohio; Dartmouth Medical School, Hanover, N. H., 1896; member of the Ohio State Medical Association; served during the World War; for many years member of the city council; aged 66; died, Nov. 5, 1940.

**Thomas F. Conn**, Monticello, Miss.; Medical Department of Tulane University of Louisiana, New Orleans, 1906; member of the Mississippi State Medical Association; county health officer; aged 60; died, Nov. 19, 1940, in a hospital at Jackson.

**Adolf Julius Drtina** \* Seattle; University of Pittsburgh School of Medicine, 1911; at one time physician in charge of the United States Government Hospital for Natives, Dillingham, Alaska; aged 51; died, Nov. 6, 1940, of coronary thrombosis.

**James F. Noble**, Custer, Ohio; Eclectic Medical Institute, Cincinnati, 1891; aged 70; died, Dec. 2, 1940, in the East Side Hospital, Toledo, of injuries received when the automobile in which he was driving was struck by a train.

**Albert Sylvanus Maxson**, Milton Junction, Wis.; Chicago Medical College, 1882; formerly bank president; trustee of Milton College from 1902 to 1931; aged 83; died, Nov. 7, 1940, of arteriosclerosis and coronary thrombosis.

**George Dewey Sagera** \* Arnaudville, La.; Tulane University of Louisiana School of Medicine, New Orleans, 1929; aged 40; died, Nov. 19, 1940, in a sanatorium at Lafayette of injuries received in an automobile accident.

**James Franklin Cooper**, Edinburg, Ill.; Barnes Medical College, St. Louis, 1901; served during the World War; aged 75; died, Dec. 4, 1940, in the Decatur and Macon County Hospital, Decatur, of cerebral hemorrhage.

**Edgar Montealegre**, New York; Hahnemann Medical College and Hospital of Philadelphia, 1906; Jefferson Medical College of Philadelphia, 1908; aged 57; died, Nov. 1, 1940, of angina pectoris and coronary thrombosis.

**Caroline Herring Dennis**, St. Petersburg, Fla.; Woman's Medical College of the New York Infirmary for Women and Children, New York, 1890; aged 77; died, Nov. 25, 1940, in New York of carcinoma of the rectum.

**John Wilson Boggess Sr.**, Woodville, Ala.; Vanderbilt University School of Medicine, Nashville, Tenn., 1892; member of the Medical Association of the State of Alabama; aged 69; died, Dec. 2, 1940, of heart disease.

**George Suttle Gilder**, Carbon Hill, Ala.; Medical College of Alabama, Mobile, 1893; member of the Medical Association of the State of Alabama; aged 70; died in December 1940 of injuries received in an automobile accident.

**John Yeilding**, Hanceville, Ala.; Chattanooga (Tenn.) Medical College, 1894; veteran of the Spanish-American War; aged 78; died, Nov. 12, 1940, of acute dilatation of the heart, chronic myocarditis and nephritis.

**Swithin Chandler** Ⓢ Philadelphia; University of Pennsylvania Department of Medicine, Philadelphia, 1892; aged 70; died, Dec. 10, 1940, at his home in Strafford, Pa., of arteriosclerosis and chronic myocarditis.

**Mark Watson Emery**, Portland, Ore.; University of Oregon Medical School, Portland, 1915; aged 48; died, Nov. 27, 1940, in the Good Samaritan Hospital of rheumatic heart disease and cerebral embolism.

**François Xavier Albert Chevrier**, Ottawa, Ont., Canada; School of Medicine and Surgery of Montreal, Faculty of Medicine of the University of Laval at Montreal, 1898; aged 65; died, Oct. 16, 1940.

**Frances May Gage Hulbert**, Chicago; Hahnemann Medical College of the Pacific, San Francisco, 1895; aged 75; died, Dec. 17, 1940, of injuries received when struck by an automobile when crossing the street.

**William Stevenson MacLaren**, Princeton, N. J.; College of Physicians and Surgeons, medical department of Columbia College, New York, 1889; aged 74; died, Nov. 29, 1940, of myocardial insufficiency.

**Paul Merino Hunsicker**, Beaver Meadows, Pa.; Medico-Chirurgical College of Philadelphia, 1901; served during the World War; aged 70; died, Nov. 21, 1940, in the Hazleton (Pa.) State Hospital.

**Hugh Francis Bradley**, Jarrettsville, Md.; University of Maryland School of Medicine, Baltimore, 1897; aged 71; died in December 1940 of coronary thrombosis, arteriosclerosis and chronic cholecystitis.

**William E. Menefee**, Cleburne, Texas; Medical Department of Tulane University of Louisiana, New Orleans, 1888; member of the State Medical Association of Texas; aged 83; died, Nov. 13, 1940.

**Moses Eason Sherer**, Portland, Ore.; Chattanooga (Tenn.) Medical College, 1908; served during the World War; on the staff of the Veterans Administration Facility; aged 57; died, Nov. 29, 1940.

**John Evans Hanna Jr.**, Knoxville, Tenn.; University of Georgia Medical Department, Augusta, 1890; also a pharmacist; aged 76; died, Nov. 26, 1940, in St. Mary's Hospital of chronic cardiorrenal disease.

**Charles Sumner Goodwin**, Syracuse, N. Y.; New York University Medical College, New York, 1896; served during the World War; aged 66; died, Dec. 9, 1940, of lobar pneumonia.

**Victor John Ganey**, Winchester, Tenn.; Wayne University College of Medicine, Detroit, 1940; county health officer; aged 26; died, Nov. 20, 1940, in the Harper Hospital, Detroit.

**Walter James Wellington**, Rye, N. Y.; Long Island College Hospital, Brooklyn, 1896; aged 65; died, Nov. 29, 1940, in the United Hospital, Port Chester, of cerebral embolism.

**Charles Fredric Montgomery**, Los Angeles; Chicago Homeopathic Medical College, 1895; aged 72; died, Nov. 17, 1940, in the Los Angeles General Hospital of pneumothorax.

**Margaret Knickerbocker Preston** Ⓢ Syracuse, N. Y.; Syracuse University College of Medicine, 1927; aged 49; died, Nov. 24, 1940, of nephritis and rheumatic heart disease.

**Israel Trachtenberg** Ⓢ New York; College of Physicians and Surgeons, Baltimore, 1915; on the staff of the Bronx Hospital; aged 59; died, Nov. 19, 1940, of brain tumor.

**Haim Solomon Bobroff**, Chicago; University of Moscow Faculty of Medicine, Russia, 1916; aged 49; died, Dec. 16, 1940, of cyanide poisoning, self administered.

**John Ernst Nast**, San Francisco; University of California Medical Department, San Francisco, 1895; aged 78; died, Nov. 12, 1940, of myocarditis and arteriosclerosis.

**Montgomery Merritt Hannum** Ⓢ Eustis, Fla.; University of Tennessee Medical Department, Nashville, 1910; aged 55; died, Dec. 9, 1940, of coronary thrombosis.

**Ernest W. Ewell**, Rochester, N. Y.; University of Buffalo School of Medicine, 1891; veteran of the Spanish-American War; aged 70; died, Nov. 30, 1940.

**William Fisher Boddie**, Forsyth, Ga.; Meharry Medical College, Nashville, Tenn., 1906; aged 56; died, Dec. 4, 1940, in Macon of cardiovascular renal disease.

**Taylor H. Nichols**, Amory, Miss.; Howard University College of Medicine, Washington, D. C., 1904; aged 61; died, Nov. 27, 1940, of cardiac asthma.

**Alexander MacLeod Brown** Ⓢ Franklin, Pa.; University of Pennsylvania Department of Medicine, Philadelphia, 1898; aged 72; died, Nov. 26, 1940.

**Caroline Allen Jones**, San Bernardino, Calif.; Medical Department of Valparaiso University, Chicago, 1905; aged 88; died, Oct. 23, 1940, of senility.

**Edgeworth Stephens Casey**, Birmingham, Ala.; Birmingham Medical College, 1900; aged 63; died, Nov. 12, 1940, of duodenal ulcer and nephritis.

**Charles Augustus O'Connor**, Los Altos, Calif.; Cooper Medical College, San Francisco, 1900; aged 64; died in November 1940 of cerebral hemorrhage.

**Zachary Joseph Clark** Ⓢ Cherokee, Okla.; Kansas City (Mo.) Medical College, 1900; aged 72; died, Nov. 14, 1940, of carcinoma of the colon.

**George William Roos** Ⓢ Wellsville, N. Y.; University of Buffalo School of Medicine, 1887; aged 73; died, Nov. 5, 1940, of coronary thrombosis.

**Arthur Jay Sprague**, Los Angeles; Northwestern Ohio Medical College, Toledo, 1888; aged 88; died, Nov. 28, 1940, of cerebral hemorrhage.

**William Arthur Smythe**, Stroudsburg, Pa.; University of Pennsylvania School of Medicine, Philadelphia, 1911; aged 52; died, Nov. 22, 1940.

**John A. Mercer**, Chilton, Texas; Medical Department of Tulane University of Louisiana, New Orleans, 1887; aged 79; died, Nov. 17, 1940.

**James Fred Rigg**, Niagara-on-the-Lake, Ont., Canada; University of Toronto Faculty of Medicine, 1911; aged 52; died, Nov. 14, 1940.

**Edward Daniel Burtt** Ⓢ Lincoln, N. H.; Baltimore Medical College, 1900; aged 69; died, Dec. 3, 1940, of cerebral hemorrhage and heart disease.

**Alexander Ardell Jackson**, Toronto, Ont., Canada; University of Toronto Faculty of Medicine, 1904; aged 64; died, Nov. 16, 1940.

**Charles H. Ashton**, Franklin, Pa.; Baltimore Medical College, 1905; aged 61; died in November 1940 of cerebral thrombosis.

**Arthur Gladstone Wallis**, St. Catharines, Ont., Canada; University of Toronto Faculty of Medicine, 1905; died, Nov. 18, 1940.

**Herman C. W. Gresens** Ⓢ Chicago; Rush Medical College, Chicago, 1897; aged 71; died, Nov. 28, 1940, of heart disease.

**Albert G. Austell**, Center, Okla.; Memphis (Tenn.) Hospital Medical College, 1906; aged 80; died, Oct. 28, 1940, of heart disease.

**Pryse Campbell Park**, Durham, Ont., Canada; McGill University Faculty of Medicine, Montreal, 1888; died, Nov. 1, 1940.

**C. M. H. Farrar**, Hillsboro, Tenn.; Nashville Medical College, 1878; aged 92; died, Nov. 11, 1940, of acute nephritis.

**Donald Albert Cameron**, London, Ont., Canada; Trinity Medical College; Toronto, 1895; aged 69; died, Oct. 19, 1940.

**Richard Arthur Byrd**, Edmond, Okla.; Hospital College of Medicine, Louisville, Ky., 1907; aged 58; died, Nov. 18, 1940.

**William H. Martin**, Winter Haven, Fla.; Fort Wayne (Ind.) College of Medicine, 1887; aged 78; died, Nov. 19, 1940.

**W. A. Walden**, Davisboro, Ga.; Atlanta Medical College, 1893; aged 70; died, Nov. 20, 1940, of bronchopneumonia.

**William Kerr**, Toronto, Ont., Canada; Trinity Medical College, Toronto, 1889; aged 81; died, Nov. 18, 1940.

**Clyde Ware Swank**, Chicago; Rush Medical College, Chicago, 1890; aged 76; died, Dec. 6, 1940, of carcinoma.

**J. L. Shirley**, Chattanooga, Tenn.; Chattanooga Medical College, 1896; aged 82; died, Nov. 9, 1940.

**Lewis F. Hamrick**, Baltimore; Baltimore Medical College, 1901; aged 64; died in November 1940.

## Bureau of Investigation

### ANOTHER IMPOSTOR REPEATS

#### Aaron Raffelson Found Using Name of New York Physician

In 1934 the Bureau of Investigation published in *THE JOURNAL* an article dealing with one Aaron W. Raffelson, impostor. Within the past year some one, identified by several as this same Raffelson, has been trying similar activities with a little different approach. This time, instead of using one of his aliases (Aaron Raphael, Donald Clinton Raphael, Aaron Wolf, C. S. Julian, Donald B. Parkinson, Sam Clarkson Parkinson, H. C. Mathers and Aaron Raphaelson) he "borrowed" the name of a New York physician. In previous instances—in New York in 1930 and in Santa Fe, N. M., in 1934—he claimed medical education at New York University, University and Bellevue Hospital Medical College, the University of Oregon Medical School and the State University of Iowa College of Medicine.

The more recent incident occurred at Denver and, needless to say, the impostor claimed as his education that of a prominent New York physician whom he was impersonating. In both instances there was a claim for specialization in psychiatry. The other essential facts, which were dealt with in a previous article in *THE JOURNAL*, indicate that in 1934 Raffelson was about 23 but looked older, was 5 feet 5½ inches tall, weighed 130 pounds,



Photographs of Raffelson (taken in 1930) published in *THE JOURNAL* for Dec. 1, 1934, which a Denver physician states are unmistakably those of the individual referred to in this article.

was slim and wiry in build, sometimes wore his hair bright red and other times black, had dark brown eyes, a swarthy complexion, occasionally wore a mustache and invariably went bareheaded. Also mentioned was a fingerprint classification in connection with his arrest for forgery in New York City in 1930. This read 9 U  
21 Ra 14

In 1934, just as New York officials were about to close in on him again, he left for Santa Fe, N. M. There he spoke on psychiatry before local civic clubs and assisted in the investigation of a murder committed in Santa Fe, testifying under oath that he was a practicing physician and that he had assisted in conducting an autopsy on the deceased. Shortly thereafter he left Santa Fe in an automobile which he had obtained by depositing a worthless check. In view of the fact that the car was later found in El Paso, Texas, it was assumed that he had crossed the Mexican border.

During the past year in Colorado, an individual who has been identified as this same person called at the office of the state board of medical examiners with regard to obtaining a license to practice medicine on the basis of his New York license. When he was told that he must meet the requirements of the Colorado Basic Science Board before he would be eligible to file an application, he did not make any attempt to submit credentials. At about this time he opened an office in Denver and distributed professional cards containing the name of the New York physician and the following legend under the name: "Practice limited to Psychometrics—Child Guidance—By appointment only." As soon as the state authorities obtained

this information, he was asked to close his office, which he did. In the meantime, however, he had applied to and had received permission to be admitted to the lecturing staff at the University of Colorado School of Medicine. Subsequently he was again found seeing patients professionally and was informed by the superintendent of a local hospital that he must make application to the staff before he could visit such patients. He filled out a form, using the data of the New York physician whom he was impersonating. In that connection, it developed that the real doctor was still located in New York and actively on duty there. When the impostor was asked to appear before the medical advisory board at the hospital, he attempted to reclaim his application and promptly disappeared from sight, supposedly once again in the direction of the Mexican border.

The files of the Bureau of Investigation contain the names of individuals who have frequently repeated their activities as impostors. With each new offense, publicity is given to them in the hope that the publication of their pictures and the data concerning them will militate against their repeating their performances elsewhere. Most of them, however, are able to get away with repeated offenses of this nature because they permit sufficient time to pass so that few physicians recall the incident.

One important factor which aids these frauds in imposing on the profession and the public is the reasonable assumption on the part of the members of the profession that medicine is such an intricate and detailed science that one who did not possess a knowledge of medicine could not pretend to that knowledge without being discovered almost immediately. Apparently in the present instance a superficial knowledge of science enabled this impostor to pass himself off for a time in Colorado not only as a physician but as a specialist in psychiatry.

### MISBRANDED "PATENT MEDICINES"

#### Abstracts of Notices of Judgment Issued by the Food and Drug Administration of the United States Department of Agriculture

[EDITORIAL NOTE.—The abstracts that follow are given in the briefest possible form: (1) the name of the product; (2) the name of the manufacturer, shipper or consigner; (3) the composition; (4) the type of nostrum; (5) the reason for the charge of misbranding and (6) the date of issuance of the Notice of Judgment—which is considerably later than the date of the seizure of the product and somewhat later than the conclusion of the case by the Food and Drug Administration.]

**Acetodyne Tablets.**—Glens Falls Pharmacal Co., Inc., (New York State). Composition: declared on label to contain 2 grains of acetophenetidin per tablet, whereas it possessed none of this drug but did contain 1.91 grains of acetanilid, from which acetophenetidin is derived, but which was not declared on the label; hence misbranded because of false labeling.—[N. J. 30979; August 1941.]

**Anti-Rheumatic Fever Compound.**—Modern Drugs, Inc., Philippi, W. Va. Composition: essentially plant drugs, including an alkaloid-bearing drug, small amounts of sodium salicylate, potassium acetate, potassium iodide, alcohol, sugar and water. For rheumatic fever, various forms of rheumatic and muscular pains. Fraudulent therapeutic claims.—[N. J. 30978; August 1940.]

**Camfo-Phenol Lotion.**—Modern Drugs, Inc., Philippi, W. Va. Composition: essentially camphor, phenol (31.7 per cent by weight in one sample and 35.5 per cent by weight in the other) with alcohol and iodine. Fraudulently represented as a treatment for infection, wounds, abscesses, boils, burns and ulcers of syphilis, tuberculosis and other debilitating diseases.—[N. J. 30978; August 1940.]

**Enrich Organic Iron Hematinic.**—Tam Products, Inc., New York. Composition: essentially small amounts of an extract of an animal product, compounds of sodium and ammonium, chlorides, sulfates and phosphates, a trace of an iron compound, glycerin and water. Biologic tests showed it to contain not more than 2 international units of vitamin B<sub>12</sub> per cubic centimeter and not more than 240 Chase-Sherman units of vitamin B<sub>12</sub> per fluid ounce. Name falsely represented the article to contain a substantial amount of organic iron; fraudulently represented to enrich blood with iron and to benefit nerves, blood, digestion, vitamin B deficiency; and some other things.—[N. J. 30997; August 1940.]

**Ethacaine.**—Seydel Chemical Co., Jersey City, N. J. Composition: essentially benzoic acid and benzocaine in a petrolatum base, with oxyquinoline present. Not antiseptic when used as directed and hence misbranded as such; further misbranded because fraudulently represented as an effective treatment of ulcers and other skin disorders, for the relief of pain in ulcers and a cure for these and superficial carcinomas, also for relief of itching in eczema and for the quick healing of lesions.—[N. J. 30981; August 1940.]

## Medical Examinations and Licensure

### COMING EXAMINATIONS

#### NATIONAL BOARD OF MEDICAL EXAMINERS EXAMINING BOARDS IN SPECIALTIES

Examinations of the National Board of Medical Examiners and Examining Boards in Specialties were published in *THE JOURNAL*, January 25, page 330.

#### BOARDS OF MEDICAL EXAMINERS

ALABAMA: Montgomery, June 17-19. Sec., Dr. J. N. Baker, 519 Dexter Ave., Montgomery.

ARKANSAS: \* *Medical*. Little Rock, June 5-6. Sec., Dr. D. L. Owens, Harrison, *Eclectic*. Little Rock, June 5-6. Sec., Dr. Clarence H. Young, 1415 Main St., Little Rock.

CALIFORNIA: *Oral examination* (required when reciprocity application is based on a state certificate or license issued ten or more years before filing application in California), San Francisco, April 16. *Written*. Los Angeles, Feb. 24-27. Sec., Dr. Charles B. Pinkham, 1020 N St., Sacramento.

CONNECTICUT: \* *Medical*. *Written*. Hartford, March 11-12. *Endorsement*. Hartford, March 25. Sec., Dr. Thomas P. Murdock, 147 W. Main St., Meriden. *Homoeopathic*. Derby, March 11-12. Sec., Dr. Joseph H. Evans, 1488 Chapel St., New Haven.

DELAWARE: July 8-10. Sec., Medical Council of Delaware, Dr. Joseph S. McDaniel, 229 S. State St., Dover.

DISTRICT OF COLUMBIA: \* Washington, May 12-13. Sec., Commission on Licensure, Dr. George C. Ruhland, 203 District Bldg., Washington.

FLORIDA: \* Jacksonville, June 23-24. Sec., Dr. William M. Rowlett, Box 786, Tampa.

GEORGIA: Atlanta, June. Sec., State Examining Boards, Mr. R. C. Coleman, 111 State Capitol, Atlanta.

IDAHO: Boise, April 1. Dir., Bureau of Occupational License, Mr. H. B. Whittlesey, 335 State Capitol Bldg., Boise.

INDIANA: Indianapolis, June 17-19. Sec., Board of Medical Registration and Examination, Dr. J. W. Bowers, Citizens Trust Bldg., Fort Wayne.

KANSAS: Kansas City, June 17-18. Sec., Board of Medical Registration and Examination, Dr. J. F. Hassig, 905 N. 7th St., Kansas City.

KENTUCKY: Louisville, June 5-7. Sec., State Board of Health, Dr. A. T. McCormack, 620 S. Third St., Louisville.

MAINE: Portland, March 11-12. Sec., Board of Registration of Medicine, Dr. Adam P. Leighton, 192 State St., Portland.

MARYLAND: *Medical*. Baltimore, June 17-20. Sec., Dr. John T. O'Mara, 1215 Cathedral St., Baltimore. *Homoeopathic*. Baltimore, June 17-18. Sec., Dr. John A. Evans, 612 W. 40th St., Baltimore.

MASSACHUSETTS: Boston, March 11-13. Sec., Board of Registration in Medicine, Dr. Stephen Rushmore, 413-F State House, Boston.

MICHIGAN: \* Ann Arbor and Detroit, June 11-13. Sec., Board of Registration in Medicine, Dr. J. Earl McIntyre, 202-4 Hollister Bldg., Lansing.

MISSISSIPPI: Jackson, June. Asst. Sec., State Board of Health, Dr. R. N. Whitfield, Jackson.

MONTANA: *Reciprocity*. Helena, March 31. *Written*. Helena, April 1. Sec., Dr. S. A. Cooney, 216 Power Block, Helena.

NEVADA: *Reciprocity with oral examination*, Feb. 3. Sec., Dr. Fred M. Anderson, 215 N. Carson St., Carson City.

NEW HAMPSHIRE: Concord, March 13-14. Sec., Board of Registration in Medicine, Dr. T. P. Burroughs, State House, Concord.

NEW JERSEY: Trenton, June 17-18. Sec., Dr. Earl S. Hallinger, 28 W. State St., Trenton.

NEW MEXICO: Santa Fe, April 14-15. Sec., Dr. Le Grand Ward, 135 Senn Plaza, Santa Fe.

VERMONT: Burlington, Feb. 11. Sec., Dr. W. Scott Nay, Underhill.

WEST VIRGINIA: Charleston, March 3. Sec., Public Health Council, Dr. Arthur E. McClue, State Capitol, Charleston.

WYOMING: Cheyenne, Feb. 3-4. Sec., Dr. M. C. Keith, Capitol Bldg., Cheyenne.

\* Basic Science Certificate required.

#### BOARDS OF EXAMINERS IN THE BASIC SCIENCES

ARIZONA: Tucson, March 18. Sec., Mr. Franklin E. Roach, Science Hall, University of Arizona, Tucson.

COLORADO: March 6-7. Sec., Dr. Esther B. Starks, 1459 Ogden St., Denver.

CONNECTICUT: Feb. 8. Address State Board of Healing Arts, 1945 Yale Station, New Haven.

DISTRICT OF COLUMBIA: Washington, April 21-22. Sec., Commission on Licensure, Dr. George C. Ruhland, 203 District Bldg., Washington.

FLORIDA: De Land, June 7. *Applications must be on file not later than May 24*. Sec., Prof. J. F. Conn, John B. Stetson University, De Land.

MICHIGAN: Ann Arbor, Detroit and East Lansing, Feb. 14-15. Sec., Miss Flora E. Dube, East Lansing.

OREGON: Portland, Feb. 15. Sec., State Board of Higher Education, Mr. Charles D. Byrne, University of Oregon, Eugene.

RHODE ISLAND: Providence, Feb. 19. Sec., Division of Examiners, Rev. Nicholas H. Serror, Providence College, Providence.

SOUTH DAKOTA: June. Sec., Dr. G. M. Evans, Yankton.

WISCONSIN: Madison, April 5. Sec., Prof. Robert N. Bauer, 3414 W. Wisconsin Avenue, Milwaukee.

### Arizona October Report

Dr. J. H. Patterson, secretary, Arizona State Board of Medical Examiners, reports the written examination for medical licensure held at Phoenix, October 1-2, 1940. The examination covered 10 subjects and included 100 questions. An average of 75 per cent was required to pass. Six candidates

were examined, all of whom passed. Four physicians were licensed to practice medicine by reciprocity. The following schools were represented:

School	PASSED	Year Grad.	Per Cent
University of California Medical School.....	(1939)	82.2*	
Rush Medical College.....	(1938)	85.2	
University of Illinois College of Medicine.....	(1940)	78.1	
Johns Hopkins University School of Medicine.....	(1939)	83.2	
St. Louis University School of Medicine.....	(1938)	88.3	
Columbia Univ. College of Physicians and Surgeons.....	(1938)	76.5	
		81.8	

School	LICENSED BY RECIPROCITY	Year Grad.	Reciprocity with
Rush Medical College.....	(1930)		Illinois
State University of Iowa College of Medicine.....	(1934)		Iowa
Tulane University of Louisiana School of Medicine.....	(1936)		Louisiana
University of Wisconsin Medical School.....	(1934)		Wisconsin

### Connecticut July Report

Dr. Thomas P. Murdock, secretary, Connecticut Medical Examining Board, reports the written examination for medical licensure held at Hartford, July 9-10, 1940. The examination covered 9 subjects and included 70 questions. An average of 75 per cent was required to pass. Thirty-six candidates were examined, 17 of whom passed and 19 failed. The following schools were represented:

School	PASSED	Year Grad.	Per Cent
Yale University School of Medicine.....	(1940)	75.1*	82.2*
George Washington University School of Medicine.....	(1938)		75
Georgetown University School of Medicine.....	(1939)		75.1*
Loyola University School of Medicine.....	(1940)		75
Louisiana State University School of Medicine.....	(1940)		78.4
Harvard Medical School.....	(1938)		76.4
Tufts College Medical School.....	(1939)		80.4
Cornell University Medical College.....	(1940)		80.7
New York University College of Medicine.....	(1940)		75.1
Syracuse University College of Medicine.....	(1940)		77.1
University of Cincinnati College of Medicine.....	(1939)		75.3
Temple University School of Medicine.....	(1940)		77
Medizinische Fakultät der Universität Weip.....	(1937)		75.7
Friedrich-Wilhelms-Universität Medizinische Fakultät Berlin.....	(1936)		77
Universität Leipzig Medizinische Fakultät.....	(1927)		75.8
Universität Bern Medizinische Fakultät.....	(1936)		76.1

School	FAILED	Year Grad.	Number Failed
Marquette University School of Medicine.....	(1940)		1
University of Western Ontario Medical School.....	(1938)		1
Laval University Faculty of Medicine.....	(1931)		1
Medizinische Fakultät der Universität Wein.....	(1934), (1936), (1937), (1938)		4
Eberhard-Karls-Universität Medizinische Fakultät, Tübingen.....	(1920)		1
Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin.....	(1924)		1
Ludwig-Maximilians-Universität Medizinische Fakultät, München.....	(1925)		1
Universität Heidelberg Medizinische Fakultät.....	(1920)		1
Universität Leipzig Medizinische Fakultät.....	(1932)		1
Magyar Királyi Erzsébet Tudományegyetem Orvostudományi, Pecs.....	(1932)		1
Magyar Királyi Pázmány Petrus Tudományegyetem Orvosi Fakultasa, Budapest.....	(1938)		1
Regia Università degli Studi di Bologna. Facoltà di Medicina e Chirurgia.....	(1937)		1
Regia Università degli Studi di Roma. Facoltà di Medicina e Chirurgia.....	(1937)		1
Universität Bern Medizinische Fakultät.....	(1937)		1
Osteopaths †.....			2

Twenty-seven physicians were successful in the oral examination held for endorsement applicants at Hartford, July 23. The following schools were represented:

School	PASSED	Year Grad.	Endorsement of
Yale University School of Medicine.....	(1934), (1938, 2), (1939, 4)		N. B. M. Ex. Iowa
George Wash. Medical College.....	(1908)		
The School of Medicine.....	(1937)*		New York
Logical Science.....	(1937)		Louisiana
Tulane University.....	(1937)		Maryland
Johns Hopkins.....	(1936)		N. B. M. Ex.
Boston University School of Medicine.....	(1936)		N. B. M. Ex.
Harvard Medical School.....	(1936)		N. B. M. Ex.
University of Michigan Medical School.....	(1937)		N. B. M. Ex.
Albany Medical College.....	(1939)		N. B. M. Ex.
Columbia University College of Physicians and Surgeons.....	(1935) N. B. M. Ex., (1937)		New York
Long Island College Hospital.....	(1927)		New York
University of Rochester School of Medicine and Dentistry.....	(1936)		New York
University of Tennessee College of Medicine.....	(1931)		Tennessee
Baylor University College of Medicine.....	(1936)		Texas
University of Vermont College of Medicine.....	(1935)*		N. B. M. Ex.
(1937)* Vermont.....			
University of Manitoba Faculty of Medicine.....	(1935)		Maryland
University of Glasgow Medical Faculty.....	(1934)*		New York

\* License has not been issued.

† One examined in medicine, the other in medicine and surgery.

## Miscellany

### ACTIVITIES OF NATIONAL FOUNDATION FOR INFANTILE PARALYSIS

The first annual medical meeting of the National Foundation for Infantile Paralysis was held in New York early in November 1940.<sup>1</sup> This meeting was attended by members of the medical advisory committees, the grantees of the foundation, and the board of trustees. Reports on several studies on poliomyelitis virus were made by various investigations supported by the foundation. Virus infected material obtained from the spinal cords of monkeys has been concentrated so that the infection can be produced in dilution of one part to ten million. Studies of the purified and concentrated virus led one investigator to conclude that the virus is protein in nature or contains protein material. Poliomyelitis virus has been found in stools of patients, in contacts and in sewage collected from epidemic areas. Healthy carriers have been found in institutional outbreaks. Attempts to produce infection with poliomyelitis virus in animals other than the monkey have led to confirming previous observations to the effect that the Lansing strain could be made to produce infection in various cotton rats. All but one investigator reported that only this one strain could be made to produce the disease in the cotton rat. He however succeeded in growing several other old as well as newly isolated strains in this species of rat. It was also demonstrated that the virus could be routinely recovered from the central nervous tissue of fatal human cases and from experimental animals and that excepting for tonsils, adenoids and lymph gland tissue no other part of the body was shown to harbor the infection.

So far all attempts at producing immunity, both active and passive, have met with failure. Likewise no chemical agent has been found which will do for poliomyelitis what sulfanilamide and its derivatives have done for certain bacterial infections.

Some studies were reported indicating that the muscular fibrillation resulting from nerve destruction is not the primary cause of atrophy of paralyzed muscle. This point, however, is still controversial. One group of workers reported that occasionally muscles developed a handlike form of degeneration and that when mattress sutures were used to connect the muscle above and below these bands good functional results could be obtained. Several guides for more accurately testing muscle strength were devised and discussed.

It was concluded from one set of observations that, if the maximum benefits of physical therapy are to be secured for patients after having poliomyelitis, they must be under such care within six months of the onset. They further showed that 97 per cent of all weakened or paralyzed muscles regained the maximum possible strength within eighteen months after onset of treatment. These observations were confirmed by another investigator, who concluded additionally that rest with physical therapy in the hospital has no advantage over family treatments given in the home and that hospital care over long periods is of decided advantage only when underwater treatments are used. Observations on monkeys emphasize the value of rest treatment, since they showed that these animals when forced to exercise during the active disease process had not only a greater amount of paralysis but also a higher death rate.

In addition to these activities largely sponsored by the foundation, studies of epidemics have been made in a few areas and certain assistance has been supplied to communities and hospitals by making splints, Bradford frames and respirators available. Educational activities have been conducted and include an exhibit at the New York World's Fair viewed by more than five million persons and scholarships made available through the National Research Council. At the November meeting additional grants were recommended for continuation of existing studies or for new investigations in the amount of \$137,350.

1. Report of the First Annual Medical Meeting of the National Foundation for Infantile Paralysis.

## Bureau of Legal Medicine and Legislation

### MEDICOLEGAL ABSTRACTS

**Malpractice: Fragment of Extracted Tooth Lodged in Lung; Res Ipsa Loquitur.**—The plaintiff went to the defendant, an exodontist, on July 3, 1936 for the purpose of having six teeth extracted. At the time of the extractions the plaintiff and the defendant were alone in the defendant's office. The plaintiff was seated in the dental chair and a general anesthetic was administered. When he recovered consciousness the six teeth had been extracted. After he came out from under the anesthetic he noted a heaviness in the right side of the chest which became progressively worse. It was more of an ache than a pain, and the plaintiff felt as though he were taking cold. That evening he commenced to cough and the cough and pain increased in intensity. Two days later he returned to the defendant's office for an examination and the defendant then informed him that he had had "a hard set of teeth to pull" and that they had been broken up quite badly. The coughing and pain continued unabated until April 6, 1937, during which time the plaintiff had suffered many severe hemorrhages from his lungs, the first hemorrhage occurring in December 1936, and he lost about 60 pounds (27.2 Kg.). While eating breakfast on the morning of April 6, he choked and strangled and, after a violent spasm of coughing, he expectorated into a receptacle a quantity of blood and mucus from his lungs which material on examination by his wife was found to contain the root of a tooth. In a subsequent action for damages brought against the defendant dentist, the plaintiff alleged that the fragment of tooth had become lodged in his lung because of the defendant's negligent and unskilful conduct while the plaintiff was unconscious and wholly under the care and management of the defendant. From a directed verdict for the defendant, the plaintiff appealed to the Supreme Court of Iowa.

The defendant contended that the directed verdict was proper because the plaintiff had failed to prove any causal relationship between the alleged negligence of the defendant and the injuries of the plaintiff. The evidence showed that prior to the time the plaintiff coughed up the piece of tooth he had received treatment by many physicians and in many hospitals and had had a number of roentgenograms taken of his lungs and chest. Two of these roentgenograms, taken at St. Luke's Hospital on March 25, 1937 by a Dr. Prouty, revealed a small shadow of increased density in the base or lower posterior portion of his right lung in the region of a "posterior branch of the descending bronchus" on the right side. Dr. Prouty testified that this area of increased density might be a foreign body, or an area of calcification or fibrosis, or "superimposition of thickened bronchi." Other physicians testified in behalf of the plaintiff that his condition was the result of the lodgment of the piece of tooth in his lung. There was also substantial evidence that the plaintiff's condition developed immediately after the extractions and grew progressively worse, and that prior to July 1936 the plaintiff had been a good worker and physically sound. If, said the Supreme Court, the evidence as to the proximate cause of the plaintiff's condition is of sufficient weight, then this question should be submitted to a jury. Such evidence would not be sufficient if it showed merely that the negligence charged might fairly and reasonably have caused the injury if the circumstances shown indicated an equal probability that the injury was due to some other cause. The plaintiff, however, was not required affirmatively to disprove every possible cause of his condition which might be suggested by the defendant.

The court was of the opinion that a jury would be warranted in finding from the evidence which was adduced that the presence of the root of the tooth in the plaintiff's right lung was the proximate cause of his injury. The court believed that the

evidence supported a theory of negligence on the part of the defendant.

If the issue of the defendant's negligence were submitted to a jury, continued the court, the answer would depend largely on whether or not the doctrine of *res ipsa loquitur* applied. The defendant contended that the doctrine does not apply in a malpractice case against a physician or a dentist because negligence must be shown by the testimony of expert witnesses qualified to state what should or should not have been done. The court admitted that this was a general rule of evidence but said that when the results of an operation are such as are not to be anticipated if reasonable care had been exercised by the operator, then proof of other facts and circumstances having any fair tendency to sustain the charge of negligence will be sufficient to take the question to the jury. The court relied for its decision on *Pendergraft v. Royster*, 203 N. C. 384, 166 S. E. 285, in which the following was quoted with approval from Herzog's Medical Jurisprudence:

In many other cases it has been held that mere proof of a mistake or poor results does not itself prove malpractice, but where the injury is received while the patient is unconscious, the doctrine [of *res ipsa loquitur*] commonly is held to apply because under such circumstances the patient would not be able to testify as to what had happened, whereas the physician could.

In the present case, said the court, we have all the instrumentalities, including the unconscious body of the plaintiff, under the complete and exclusive control of the defendant dentist. We have an occurrence which, according to general knowledge and the defendant's own admission, does not happen in the ordinary course of extraction of teeth if reasonable care is used. We have also a record which might reasonably warrant a jury in finding that it did happen. There is no explanation by the defendant either that it could not have happened or that if it did happen it was through no fault of his, or that it was the fault of the plaintiff himself. The plaintiff, because of his unconscious condition, has no knowledge of what the defendant did or failed to do. Under these circumstances, concluded the court, the doctrine of *res ipsa loquitur* is applicable and a jury would be warranted in inferring therefrom that the root of the tooth passed into the plaintiff's right lung, through the failure of the defendant to exercise proper care or skill, and caused the plaintiff's injury. The court held, therefore, that the case should be submitted to the jury, and so it reversed the judgment of the lower court.—*Whetstone v. Moravec*, 291 N. W. 425 (Iowa, 1940).

**Compensation of Physicians: Right of Chief of Staff of Hospital to Collect a Personal Fee.**—The defendant, a trolley repairman, was injured in the course of his employment and was taken for treatment to a hospital at which the plaintiff physician was chief of staff or chief surgeon. The defendant's injuries consisted of bruises and contusions and fractures of the second, third, fourth and fifth lumbar vertebrae, but no surgical services were either necessitated or performed. During the defendant's stay in the hospital, Nov. 17, 1930 to Jan. 22, 1931, the plaintiff physician several times visited the ward in which the defendant had been placed but he never talked to him nor personally attended him. According to the defendant, he had no idea that the plaintiff was in any way connected with his case. The evidence showed that all services rendered to the defendant while he was in the hospital were performed by either nurses or interns and that the defendant had been placed in a ward provided for "people who cannot afford to pay." When the defendant left the hospital his entire bill, including charges for bed, board, roentgenograms, medicine and special examination, was paid by his employer. Several months later the plaintiff presented a bill for \$100 to the defendant's employer covering, supposedly, the plaintiff's charges for services rendered by him to the defendant during the first thirty days of the defendant's stay in the hospital. On the employer's refusal to pay, the plaintiff physician filed a claim before a workmen's compensation referee, but payment was again refused. He then, about two years after the defendant's discharge from the hospital, forwarded the bill for \$100 to the defendant, who likewise

refused to pay it. Finally the plaintiff brought suit against the employee to recover the amount. The jury returned a verdict for the defendant, but the trial court set the verdict aside and entered a judgment for the plaintiff. The defendant thereupon appealed to the Superior Court of Pennsylvania.

The plaintiff practically conceded that there was no express promise by the defendant to pay him for the services rendered by him but contended that the defendant was liable because of an implied promise. The plaintiff argued that this implied liability arose (1) because of the fact that the defendant was in the hospital and should have known that the medical services therein were not donated but had to be paid for by some one and (2) because he was chief of staff of the hospital. In answering the first argument the superior court stated that, while there is ordinarily an implied agreement to pay for the services of a physician, if the services were intended to be and were accepted as a gift or act of benevolence they could not at the election of the physician create a legal obligation to pay. The court pointed out that the defendant had been treated while unconscious and had been placed in a general ward. He was never treated by the plaintiff and was not sent a bill until almost two years after he left the hospital. The court held that such circumstances could not raise an implication that the defendant promised to pay the amount claimed. The court further held that the plaintiff's position as chief of staff of the hospital gave him no individual interest in the services of the interns or other members of the staff who personally attended the defendant such as to justify his making a personal charge for their services. He was not their employer nor was the hospital a private one, owned and operated by him. Hence he could have only a personal and individual claim against the defendant if he had personally rendered him some service, but, as the evidence showed, he had never personally attended him. The judgment for the plaintiff was therefore reversed.—*Pfeiffer v. Kraske*, 11 A. (2d) 555 (Penn., 1940).

**Charitable Hospitals: Liability for Tort When Covered by Insurance.**—The defendant charitable hospital was insured against all liability for the torts of its agents in the conduct of its business. In a suit against the hospital for damages for negligence in the care and treatment of a pay patient, the specific question for determination was whether a charitable institution is immune from tort liability even though a judgment against it would not jeopardize the trust fund but would be limited to funds derived from indemnity insurance. The Supreme Court of Colorado, in reversing a judgment for the defendant hospital, held, as it had held in prior cases, that the trust fund rule did not bar a judgment against a charitable institution but barred only a levy of execution against any property which was a part of the charitable trust. The fact that the defendant had insurance, therefore, merely made a judgment collectible but neither increased nor diminished the liability itself.—*O'Connor v. Boulder Colorado Sanitarium Ass'n*, 96 P. (2d) 835 (Colo., 1939).

## Society Proceedings

### COMING MEETINGS

Annual Congress on Medical Education and Licensure, Chicago, Feb. 17-18. Dr. W. D. Cutter, 535 North Dearborn St., Chicago, Secretary.

American Orthopsychiatric Association, New York, Feb. 20-22. Dr. Norville C. La Mar, 149 East 73d Street, New York, Secretary.

Central Surgical Association, Ann Arbor, Mich., Feb. 28-March 1. Dr. George M. Curtis, Ohio State University, Columbus, Ohio, Secretary.

Mid-South Post-Graduate Medical Assembly, Memphis, Tenn., Feb. 11-14. Dr. A. F. Cooper, Goodwyn Institute Bldg., Memphis, Tenn., Secretary.

Pacific Coast Surgical Association, Los Angeles, Feb. 19-22. Dr. H. Glenn Bell, University of California Hospital, San Francisco, Secretary.

Society of University Surgeons, St. Louis, Feb. 14-15. Dr. Frank Glenn, 525 East 68th St., New York, Secretary.

Western Section, American Laryngological, Rhinological and Otolaryngological Society, San Francisco, Feb. 1-2. Dr. Robert C. Martin, 384 Post St., San Francisco, Chairman.



## Current Medical Literature

### AMERICAN

The Association library lends periodicals to members of the Association and to individual subscribers in continental United States and Canada for a period of three days. Three journals may be borrowed at a time. Periodicals are available from 1930 to date. Requests for issues of earlier date cannot be filled. Requests should be accompanied by stamps to cover postage (6 cents if one and 18 cents if three periodicals are requested). Periodicals published by the American Medical Association are not available for lending but can be supplied on purchase order. Reprints as a rule are the property of authors and can be obtained for permanent possession only from them.

Titles marked with an asterisk (\*) are abstracted below.

#### Alabama State Medical Assn. Journal, Montgomery

10:157-188 (Nov.) 1940

- More Recent Ideas in Treatment of Burns. L. Noland and C. H. Wilson, Fairfield.—p. 157.  
The Newborn as a Pediatric Entity. J. R. Garber, Birmingham.—p. 162.  
Sulfanilamide and Its Derivatives. D. C. Haisten, Dothan.—p. 166.  
Urinary Infections in Children. J. P. Robertson, Birmingham.—p. 170.

#### American Journal of Cancer, New York

39:463-614 (Aug.) 1940

- Endogenic Blastogenic Substances. H. E. Kleinenberg, S. A. Neufach and L. M. Shahad, Leningrad, Soviet Union.—p. 463.  
Production of Benign and Malignant Skin Tumors in Mice Painted with Bantu Liver Extracts. M. J. A. des Ligneris, Johannesburg, South Africa.—p. 489.  
Examination of Human Tissue for Carcinogenic Factors. I. Hieger, London, England.—p. 496.  
Cytology of 1, 2, 5, 6-Dibenzanthracene Mouse Tumors. M. Levine and H. Bergmann, New York.—p. 504.  
Chemical Compounds as Carcinogenic Agents: Second Supplementary Report: Literature of 1938 and 1939. J. W. Cook and E. L. Kennaway, Glasgow, Scotland.—p. 521.

#### Am. J. Roentgenol. & Rad. Therapy, Springfield, Ill.

44:645-804 (Nov.) 1940

- Specialization Within Roentgenology. M. C. Sosman, Boston.—p. 645.  
Some Aspects of Biologic Action of Ionizing Radiations. G. Failla, New York.—p. 649.  
Adolescent Development of Sella Turcica and Frontal Sinus Based on Consecutive Roentgenograms. C. B. Davenport, Cold Spring Harbor, N. Y., and Olive Renfro, Thiells, N. Y.—p. 665.  
Use of Thorium Dioxide in Roentgenography of Sinuses. R. C. Grove and R. A. Cooke, New York.—p. 680.  
\*Acute Mediastinitis: Roentgenologic, Pathologic and Clinical Features and Principles of Operative Treatment. H. Neuhof and C. B. Rabin, New York.—p. 684.  
Roentgenologic Differentiation of Rheumatic from Nonrheumatic Mitral Valve Calcifications. B. S. Epstein, Brooklyn.—p. 704.  
\*Prognosis in Silicosis. J. T. Farrell Jr., M. J. Sokoloff and R. Charr, Philadelphia.—p. 709.  
Epiphyal Bone: Consideration of Some Small Accessory Bones of Neck. W. A. Evans Jr., Detroit.—p. 714.  
Leiomyosarcoma of Fundus of Stomach with Perforation. M. Mass and J. D. Kirshbaum, Chicago.—p. 716.  
Persistence of Notochord. G. R. Krause, Cleveland.—p. 719.  
Fractures of Spine After Metrazol Convulsive Therapy and Other Convulsive States. M. M. Pearson and H. W. Ostrum, Philadelphia.—p. 726.  
Study of Bone Metastases from Carcinoma of Prostate. J. H. Marks, Boston.—p. 732.  
Radium Treatment of Rodent Ulcer Near Eye. A. A. Charteris, Glasgow, Scotland.—p. 737.  
Radium Treatment of Vascular Nevi: Analysis of 152 Cases Seen During 1928-1938. E. A. Poble and J. B. McNaney, Madison, Wis.—p. 747.  
Effect of Roentgen Irradiation on Lymphatic Transport of India Ink. E. D. Sugarbaker and K. Sugiura, New York.—p. 756.

**Acute Mediastinitis.**—Neuhof and Rabin collected 67 cases from the records of the Mount Sinai Hospital for a period of ten years. Acute infections of the pharynx and injuries to the esophagus accounted for more than three fourths of the cases. In acute mediastinal lymphadenitis no abnormalities, as a rule, are discernible on the film. When the nodes are greatly enlarged they may cause a widening of the mediastinal shadow. Occasionally the enlarged paratracheal nodes may be observed as discrete shadows. A marked widening of the superior mediastinal shadow with bulging borders, simulating an expanding abscess, may be caused by large suppurating mediastinal lymph nodes which are matted together. Roentgenograms in oblique position may occasionally disclose inflamed lymph nodes. Roentgenograms in the early stages of phlegmonous mediastinitis may not disclose any abnormality. In most cases there is a diffuse

widening of the superior mediastinal shadow. In suspected cases, films of the neck in the lateral position, a widened retrotracheal (prevertebral) shadow may infer the diagnosis. The earliest stages of abscess of the upper mediastinum may simulate phlegmonous mediastinitis, but the rapid widening of the shadow and a bulging border usually establish the diagnosis. An abscess of the lower mediastinum that extends to the right side causes a semicircular shadow to project into the right pulmonary field. An abscess which extends to the left may be overlooked because of its relation to the heart. In mediastinal abscess with perforation of the esophagus a widened mediastinal shadow following an accident capable of causing esophageal perforation is presumptive evidence. Similarly roentgen evidence of mediastinal or subcutaneous emphysema following such an injury is indirectly indicative. The early picture of a localized area of pneumonic consolidation adjacent to the mediastinum. The fulminating cases presented the rare textbook picture of overwhelming sepsis or, more commonly, dysphagia, dyspnea and later severe "pneumonia." Throat infection with or without a retropharyngeal abscess or esophageal trauma was the etiologic factor. Cases of moderate severity either of nontraumatic or of traumatic origin were fatal when the source was nonsuppurative or, if suppurative, when the causative abscess had not been evacuated adequately. The duration was from a week to a month or longer. Beginning with sore throat, fever and chill in the nontraumatic group, and with pain in the neck and chest, dysphagia and fever in the traumatic, the course in both was characterized by moderate toxemia and dysphagia. A deceptive remission occurred in the fatal cases. The relatively mild cases presented a suppurative mediastinal lesion, usually a well localized abscess. In all cases an abscess in the cervical region had been present, and fever had continued without a discernible local cause after the cervical abscess had been drained. Dyspnea, cough or pain called attention to an intrathoracic complication. Clinical manifestations referable to the mediastinal infection are not always present. Physical examination of the chest is essentially negative in most instances of acute mediastinal infection except when signs of pleural effusion or pneumonic infiltration exist. Spinal percussion tenderness is a suggestive sign. Infiltration and tenderness are often present following trauma to the cervical esophagus. The trachea is displaced forward when a mediastinal infection is derived from an infection deeply situated in the lower cervical region. The most important operative indication is prophylactic and is concerned with the lesion which frequently precedes the mediastinal infection. Exposure of and drainage to the laceration in the esophagus is indicated in most cases. Cervical infection of nontraumatic origin was the source of mediastinal infection in about one third of their cases. Adequate and timely drainage would have obviated some. The site of the collection of pus in the neck should determine the entry to the mediastinum. Drainage of the latter via the neck may possibly be adequate down to the fourth dorsal vertebra but will not be adequate below this level. A posterior mediastinotomy should be added when further descent is suspected. Exploratory puncture is probably a questionable procedure. The roentgenogram is the basic guide for correct approach to the mediastinal abscess, and no positions should be omitted from which information as to the exact site of the lesion may be obtained.

**Prognosis in Silicosis.**—Farrell and his colleagues discuss the factors which influence the prognosis of silicosis. In their study of 511 anthracite coal miners with silicosis they found that only 77 were discharged as improved, 243 as unimproved and 191 died. The ages of those who improved and those who died varied from 15 to 69 years. Most of the deaths occurred in the fifth and sixth decades and were among those who had worked from eighteen to twenty-three years. Emphysema was the most common complication and, when extensive, prognosis was unfavorable. The second most common complication was tuberculosis. The prognosis in the first and second stages of silicosis complicated by tuberculosis was the same as in non-silicotic tuberculosis, but in stage 3 it was much worse. Patients with clinical tuberculosis but with negative sputum have a better prognosis than those with clinical tuberculosis and positive sputum. The roentgen changes most suggestive of tuberculosis were asymmetrical consolidation and cavitation, regardless of

the findings in the sputum. Lobar pneumonia terminated fatally more often in patients with silicosis than in nonsilicotic patients. Heart disease, a common accompaniment of silicosis, had a characteristic clinical course and made the prognosis unfavorable. The most common type was myocardial degeneration. Miners with clinical symptoms of myocardial disease and roentgen evidence of cardiac enlargement without symptoms and toxemia usually suffered cardiac deaths. Those with clinical and roentgen signs of heart disease but with marked toxic symptoms of tuberculosis usually died of the latter disease. Spontaneous pneumothorax occurred more frequently in silicosis complicated or uncomplicated by tuberculosis than in any other pulmonary disease; it was present in 22 instances. It may be bilateral and affects the prognosis unfavorably. Carcinoma of the bronchus, not a common complication, makes the prognosis hopeless.

### Am. J. Syphilis, Gonorrhea and Ven. Dis., St. Louis

24:671-822 (Nov.) 1940

- Methods for Isolation and Cultivation of Treponemes, with Special Reference to Culture Mediums. Clara C. Kast and J. A. Kolmer, Philadelphia.—p. 671.
- Interpretation of Bruusgaard's Paper on Fate of Untreated Syphilitics. W. T. Sowder, Baltimore.—p. 684.
- Long-Term Results in Treatment of Early Syphilis. P. Padget, Baltimore.—p. 692.
- Cooperative Plan for Rapid Appraisal of Chemotherapy of Gonorrhea in the Male. O. F. Cox and J. H. Watkins, Boston.—p. 732.
- Nile Blue A Medium for Culture of Gonococcus. L. W. Gardner, Detroit.—p. 737.
- Present Day Treatment of Gonorrhea with Fever Therapy. A. I. Mann, Los Angeles.—p. 743.
- Antisyphilitic Treatment Administered by a Layman to Himself. J. L. Callaway, Durham, N. C.—p. 745.
- Transverse Diffuse Myelitis of Spinal Cord Following Intravenous Nearsphenamine: Report of Case Showing the Jarisch-Herxheimer Reaction. V. Moseley and J. L. Callaway, Durham, N. C.—p. 746.
- How Do the Officially Recognized Serologic Tests for Syphilis Rank in Specificity and Sensitivity? N. Nagle, St. Louis.—p. 750.
- Late Congenital Syphilis: Observations on Thirty-Nine Patients Over 25 Years of Age at Time of First Admission. F. R. Smith Jr., Baltimore.—p. 755.
- Outline of History of Syphilis. J. E. Kemp, Chicago.—p. 759.
- Microbiology of Syphilis: Present Status. J. S. Snow, Ann Arbor, Mich.—p. 780.

### American Review of Tuberculosis, New York

42:699-838 (Dec.) 1940

- \*Disappearance of Tubercle in Pulmonary Tuberculosis: Tuberculo-Asepsis. J. M. MacMillan, Rochester, N. Y.—p. 699.
- Pathology of Clinically Healed Tuberculous Cavities. O. Auerbach and H. Green, Staten Island, N. Y.—p. 707.
- Healing of Tuberculous Cavities. M. Pinner, New York.—p. 731.
- Angular Roentgenography of Pulmonary Apex. L. Ramo and M. J. Lustok, with technical assistance of Leone W. Stroud, Spivak, Colo.—p. 738.
- \*Tuberculous Empyema: Critical Review of 112 Consecutive Cases. J. H. Skavlem, M. L. Phelps, L. E. Baker and J. N. Christiansen, Cincinnati.—p. 747.
- Pathogenesis and Localization of Pulmonary Tuberculosis. B. L. Brock, Waverly Hills, Ky.—p. 755.
- Tuberculosis of Tongue: Report of Nine Cases. J. E. Farber, E. Friedland and W. F. Jacobs, Buffalo.—p. 766.
- Hoarseness in Tuberculosis. W. F. Hulse, Cleveland.—p. 776.
- Growth of Tubercle Bacilli in Tissues of Normal and Allergic Guinea Pigs. C. E. Woodruff and Ruby Green Kelly, Northville, Mich.—p. 782.
- Bacteriologic Diagnosis of Tuberculosis: Further Comparisons of Efficiency of Smear, Culture and Guinea Pig Inoculation in Detection of Tubercle Bacillus in Clinical Practice. H. G. Whitehead, with technical assistance of Dorothea Hilgeman, Baltimore.—p. 795.
- Sulfapyridine in Experimental Tuberculosis in Guinea Pigs. F. H. Heise and W. Steenkens Jr., Trudeau, N. Y.—p. 801.

#### Disappearance of Tubercle in Pulmonary Tuberculosis.

—MacMillan presents 3 illustrative cases of a large group who had active pulmonary tuberculosis, became inactive through treatment and died from causes other than macroscopic or microscopic tuberculosis. Such self-limiting pulmonary tuberculosis he terms pulmonary tuberculo-asepsis. He believes that the complete absence of tuberculosis at necropsy in proved cases has not been thoroughly correlated and sufficiently emphasized by clinicians and pathologists. In the 3 illustrative cases extensive and active pulmonary tuberculosis with positive sputum had at one time been present. Their clinical pictures, varying slightly in the individual case, show the symptomatology usually associated with active disease. For years they were sputum negative and at postmortem examination, outside of fibrosis, calcification, bronchiectasis and emphysema, were classified by pathologists

as not presenting classic tuberculosis. None of the usual gross or microscopic pathologic signs of tubercle formation were discovered. Tuberculosis going on to asepsis places the disease on a basis similar to other infectious diseases. The author feels that this fact is the rule and not the exception. Generally, emphysema, bronchiectasis, fibrosis and calcification, alone or in any combination, may be the only roentgen or pathologic sign of pulmonary disease. The appreciation of these observations should always include the possibility of tuberculosis being the original etiologic factor. It is the routine at the Iola Sanatorium, when such a possible case presents itself, to take a detailed history. The most frequent symptom leading to the detection of this type of case has been pulmonary hemorrhage in apparently well individuals. This usually follows some severe respiratory infection such as suppurative bronchitis, but calcification must not be forgotten. Chronic cough and sputum of many years' duration may be present, but these symptoms are usually minimized or denied although roentgenograms of the chest reveal extensive pulmonary disease. Associated symptoms (cough, sputum and dyspnea) must be studied extensively and evaluated properly. In the foreground one may note an unusual efficiency of alveolar phagocytosis, pulmonary hemorrhage or cor pulmonale, alone or in combination, as determining factors of this entity, and these warrant further study.

#### Tuberculous Empyema.—Skavlem and his associates studied

112 consecutive cases of tuberculous empyema encountered during four years at the Hamilton County Tuberculosis Hospital in Cincinnati. Parenchymal pulmonary lesions were demonstrated either by roentgenograms or by tubercle bacilli in the sputum in practically all of the cases. In a few cases empyema followed a simple pleurisy with effusion, the fluid originally being clear. During the period (1936 to 1939 inclusive) under study 898 cases of therapeutic pneumothorax were observed; empyema subsequent to the institution of the treatment developed in 94. A few cases were discovered only at necropsy. Tuberculous empyema, like pulmonary tuberculosis, is a disease of the young (66 patients from 15 to 30 years of age) and middle aged (43 from 31 to 50 years of age). Only 3 patients were more than 50 years of age. There was a decidedly higher percentage of males (78 cases) than females (34 cases). A larger percentage of male patients are admitted to the institution in the far advanced stage of pulmonary tuberculosis than female patients. Tuberculous empyema occurs more frequently in Negro patients than in white patients. The types of pulmonary lesions have been divided into chronic fibroid (22), chronic fibroid with caseous bronchopneumonia (59) and exudative (31), which is more common in the Negro. The location of the lesions seemed to have no great significance, except that many of the exudative lesions involved the basal part or the entire lung. The most frequent complication of tuberculous empyema was bronchopleural fistula, then chest wall sinus and then secondary pleural infection. Treatment was indifferent (bed rest, opiates and occasional thoracentesis), oleothorax and surgical intervention. Of the 41 patients receiving indifferent treatment, 40 died in the hospital and the remaining 1 signed out and the result is unknown. Fourteen of the 40 patients treated by oleothorax died and of the 13 patients who apparently recovered and were discharged it was often found that the lung on the affected side had completely or almost completely reexpanded. The authors believe that patients with this type of involvement owe their recovery to the obliteration of the infected pleural space by reexpansion rather than to any particular bactericidal qualities of the gomenol (aromatized oil). The remaining 13 patients are still in the institution; most of them are improved. Many of this group are Negro men whose exercise is greatly limited. The results of surgical intervention are encouraging. Of 24 patients treated by thoracoplasty 14 have recovered, 3 have died (2 of whom were very poor operative risks) and 7 are still under treatment, but all are improved with every prospect of recovery. Seven patients with secondary infection were treated by thoracotomy; 5 of them have died and 2 are still in the hospital with an uncertain future. It is dangerous to delay treatment until bronchopleural fistula and secondary infection develop. The high mortality among the patients treated indifferently demonstrates the futility of not aiding the efforts of nature. The

most satisfactory treatment appears to be extrapleural thoracoplasty. Preoperative preparation of these patients with 5 per cent gonemol in olive oil in the pleural cavity has been found beneficial.

### Annals of Surgery, Philadelphia

112:977-1146 (Dec.) 1940

- Carcinoma of Thyroid. F. H. Lahey, H. F. Hare and S. Warren, Boston.—p. 977.
- Studies Relating to Pathogenesis of Cholecystitis, Cholelithiasis and Acute Pancreatitis. J. D. Bigard and C. P. Baker, Omaha.—p. 1006.
- Question of Drainage Following Cholecystectomy. I. Abell and I. Abell Jr., Louisville, Ky.—p. 1035.
- Neurogenic Disturbances of Colon and Their Investigation by Colon-metrogram: Preliminary Report. J. C. White, M. G. Verlot and O. Ehrenthel, Boston.—p. 1042.
- Early Symptoms and Treatment of Nasopharyngeal Tumors. L. Davis and J. Martin, Chicago.—p. 1058.
- Trans thoracic Bronchotomy for Removal of Benign Tumors of Bronchi. L. Eloesser, San Francisco.—p. 1067.
- Repair of Inguinal Hernia with Transplantation of Cord to Femoral Canal: Preliminary Report. W. F. MacFee, New York.—p. 1071.
- Problem of Producing Complete and Lasting Sympathetic Denervation of Upper Extremity by Preganglionic Section. R. H. Smithwick, Boston.—p. 1085.
- Role for Surgeons in Problem of Essential Hypertension. P. Heinbecker, St. Louis.—p. 1101.
- Factors Influencing Prognosis in Osteogenic Sarcoma. B. L. Coley and J. L. Pool, New York.—p. 1114.

### Archives of Neurology and Psychiatry, Chicago

44:1155-1372 (Dec.) 1940

- \*Inheritance of Cerebral Dysrhythmia and Epilepsy. W. G. Lennox, E. L. Gibbs and F. A. Gibbs, Boston.—p. 1155.
- Neurologic Significance of Platybasia. W. A. Gustafson and E. Oldberg, Chicago.—p. 1184.
- \*Electroencephalograms of "Constitutionally Inferior" and Behavior Problem Children: Comparison with Those of Normal Children and Adults. D. B. Lindsley and Katharine Knox Cutts, East Providence, R. I.—p. 1199.
- Cerebral Metabolism in Mongolian Idiocy and Phenylpyruvic Oligophrenia. H. E. Himwich and J. F. Fazekas, Albany, N. Y.—p. 1213.
- Pallidohypothalamic Tract, or X Bundle of Meynert, in Rhesus Monkey. F. Vidal, Chicago.—p. 1219.
- Partial Thenar Atrophy. J. Romano and M. Michael Jr., Boston.—p. 1224.
- Alcoholic Cerebellar Degeneration. J. Romano, M. Michael Jr. and H. H. Merritt, Boston.—p. 1230.
- Vascular Changes in Thalamic Nuclei Undergoing Retrograde Degeneration. Y.-C. Tsang, Peiping, China.—p. 1237.
- A Thirteen Year Follow-Up Study of a Series of Cases of Verified Tumors of Brain. L. M. Davidoff, Brooklyn.—p. 1246.
- Unclassified Degenerative Disease of Central Nervous System. W. J. C. Verhaar, Batavia, Java, Netherland East Indies.—p. 1262.
- Innervation Complex of Lid and Jaw. L. Halpern, Jerusalem, Palestine.—p. 1271.
- Juvenile Familial Amaurotic Idiocy (Vogt-Spielmeyer Disease): Review of Literature and Clinical Report of Case. S. Levy, East Providence, R. I., and Olga A. G. Little, Newtown, Conn.—p. 1274.
- Cerebral Changes in Rocky Mountain Spotted Fever. G. B. Hassin, Chicago.—p. 1290.
- Aberrant Location of Subdural Hematoma. C. B. Aring and J. P. Evans, Cincinnati.—p. 1296.
- Treatment of Trigeminal Neuralgia with Vitamin B<sub>1</sub> (Thiamine Hydrochloride). A. S. Rose and B. M. Jacobson, Boston.—p. 1307.
- Element of Optical Illusion in Appearance of Preservation of Axis Cylinders in Certain Lesions of Central Nervous System. L. Alexander, Boston, and T. J. Putnam, New York.—p. 1312.

#### Inheritance of Cerebral Dysrhythmia and Epilepsy.—

Three years ago Lennox and his colleagues began to study the electroencephalographic tracings of 183 near relatives of 94 epileptic patients with cerebral dysrhythmia. The most conclusive evidence supporting the hypothesis that the electroencephalogram is of genetic value is found in the records of similar twins. Tracings from 9 pairs of normal identical twins previously secured by the Davises as well as the authors' records of 7 pairs who had some physical or neurologic abnormality are available. Six pairs of the authors' twins also had cortical dysrhythmia. In each of the 16 pairs the 2 members had similar tracings, whether the tracings were normal or abnormal. Neurologic and electroencephalographic differences existed in the records of 2 pairs of twins. This was due to an acquired cerebral lesion in 1 twin, but a similarity in the basic cortical rhythms was still present. Of the 94 patients examined, the electrical records of 4 were not secured and the records of 2 were normal. One of the patients with normal records had had only a few convulsions and the other had been free from symptoms for seventeen years. Of the relatives tested 143 were

parents, 36 were siblings and 4 were children. Tracings were made simultaneously from six areas of the cortex. Definitely abnormal records were obtained in 60 per cent of the relatives and in 10 per cent of a control group of 100 persons who had no near relative with epilepsy. In 55 families records were obtained from both parents and 35 per cent of the records of both parents were abnormal. In only 5 per cent were the records of both parents unmistakably normal. Dysrhythmia was as frequent among the relatives of patients with so-called symptomatic epilepsy as among the relatives of patients with "essential" epilepsy. It occurred more often among the relatives of female (64 per cent) than of male patients (56 per cent) and more often among female relatives (65 per cent) than among male relatives (54 per cent). The data include 5 families with similar twins with seizures or dysrhythmia. In each pair of twins there was a similarity of the fundamental rhythm, though the twins of only 1 pair had seizures. The authors believe this evidence indicates that the dysrhythmia of epilepsy is inheritable and that such a dysrhythmia may represent a predisposition to epilepsy or some allied disorder. Dysrhythmia may prove to be a dominant trait. Approximately 2.4 per cent of the near relatives of noninstitutionalized patients have a history of seizures and approximately 60 per cent of relatives have dysrhythmia; therefore the authors point out that numerically persons with the predisposition to epilepsy or an allied disorder outnumber actual epileptic subjects by about 25:1. The incidence of epilepsy in the population is about 0.5 per cent; hence persons with a predisposition to epilepsy form about 12 per cent of the population. These observations should be of practical value in the prophylaxis and eugenics of epilepsy by assisting the physician in tracing the descent of epilepsy and in advising patients and their relatives about marriage. Dysrhythmia in both parents was thirty-five times greater than the expected chance mating of two dysrhythmic persons. If a person with epilepsy marries, his chances of having epileptic offspring will be minimized if he chooses a person whose cortical electrical activity is normal. The eugenic possibilities of the subject are of great importance to the nation and the individual.

#### Electroencephalograms of Physically Inferior and Problem Children.—

Lindsley and Cutts present evidence which demonstrates that the electroencephalogram of a normal subject differs significantly from that of behavior problem and "constitutionally inferior" children. The studies were made on 36 apparently normal and healthy children from 7 to 13 years of age, 30 apparently healthy college students of superior intelligence, 50 behavior problem children from 7 to 13 years of age and 22 "constitutionally inferior" children from 7 to 13 years of age. The "constitutionally inferior" children had in general a very poor biologic, social, economic and medical heritage. They were all wards of the state and most of them were unplaceable by social agencies in foster homes. They were of dull normal or very low average mental ability, having an average intelligence quotient of 88. Simultaneous electroencephalographic recordings from four regions (right occipital, parietal, frontal and central) of the head were made of all four groups of subjects. None of the 30 college students had rhythms within 2 to 5 per second in the occipital or frontal region and only 1 showed such a rhythm in the central region. There were some children in all three groups with rhythms of this frequency; the behavior problem children were approximately twice as frequent with such rhythms as the normal or the "constitutionally inferior." For example, in the central region 52 per cent of the behavior problem children had from 2 to 5 per second waves whereas only 25 per cent of the normal group and 23 per cent of the "constitutionally inferior" group showed such rhythms. The average frequency of these rhythms was essentially the same in all groups, but the average amplitude and percentage of time were higher among the behavior problem children. The subjects with rhythms from 5 to 8 per second were from two to three times as great in the behavior problem and "constitutionally inferior" groups as in the normal groups. The average amplitude and percentage of time were also slightly greater in the former than in the latter groups. There were no significant differences in average frequency among the groups. There were no differences in the average frequency of the alpha waves (from 8 to 12 per second) among the three groups of children, but the behavior problem

and "constitutionally inferior" children had a higher average amplitude. The adult group had a higher average frequency and a lower average amplitude than the children. The percentage of time measurements for all groups ranged from 72 to 78 in the occipital, 39 to 47 in the central and 21 to 24 in the frontal region. Only a small percentage of subjects in any of the groups showed rhythms within the range of from 12 to 18 per second. There were no significant differences among the groups except that the frequency was higher among the adults. The so-called beta band (from 18 to 30 per second) showed approximately the same average frequency and range in all the groups but a lower maximal amplitude among the adults. From the data it is apparent that the higher frequency bands, from 8 to 12, 12 to 18 and 18 to 30 per second, are of no value in differentiating the three groups of children. However, there were important differences among the groups in the low frequency bands. The normal adult group showed little evidence of the 5 to 8 per second rhythms and almost complete absence of the 2 to 5 per second rhythms. The slow rhythms when present were found more frequently in the central than in the occipital or frontal region. The authors discuss the differences in the amount of abnormal slow waves among the various groups and suggest that such disturbances of cortical function are probably important factors in behavior disorders.

### Archives of Ophthalmology, Chicago

24:1077-1306 (Dec.) 1940

- Classification of Ocular Pathology. A. B. Reese, New York.—p. 1077.  
Sclerocorneal Trephining (Elliot's Operation). W. L. Benedict, Rochester, Minn.—p. 1100.  
What Is the Minimal Routine Examination of Muscles? J. W. White, New York.—p. 1113.  
Vascular Basis of Uveal Disease: Acute Anoxia as Fundamental Pathologic Physiology. W. F. Duggan, Utica, N. Y.—p. 1123.  
\*Myopia After Use of Sulfanilamide. E. A. Rittenhouse, McKeesport, Pa.—p. 1139.  
Regeneration of the Aqueous. J. G. Bellows and H. Chinn, Chicago.—p. 1144.  
Experimental Exophthalmos and Associated Myopathy Induced by Thyrotropic Extract. R. B. Aird, San Francisco.—p. 1167.  
Repeatability of Ophthalmokinometer Measurements. K. N. Ogle, H. A. Imus, L. F. Madigan, R. E. Bannon and E. C. Wilson, Hanover, N. H.—p. 1179.  
Circoid Aneurysm of Orbit; Report of Two Cases. H. R. Sniderman, Toronto, Canada.—p. 1190.  
\*Primary Pituitary Adenoma and Syndrome of Cavernous Sinus: Clinical and Anatomic Study. L. M. Weinberger, F. H. Adler and F. C. Grant, Philadelphia.—p. 1197.  
Carcinoma of Lacrimal Sac: Report of Second Case. C. N. Spratt, Minneapolis.—p. 1237.  
Unusual Changes in Lens Following Trauma: Origin and Treatment. D. M. Rolett, New York.—p. 1244.

**Myopia After Sulfanilamide.**—Rittenhouse reports a case of transitory myopia following sulfanilamide therapy and states that literature contains 6 other cases. One must determine whether the myopia was caused by the infection or by the drug or whether it is coincidental. He believes that lenticular changes probably best explain the myopia. It is conceivable that the rapid absorption of the drug can affect a transformation of the salt and water metabolism and thus cause a change in the lens which would be responsible for the refractive disturbances. Toxic irritation of the parasympathetic fibers of the ciliary muscles must be considered. Sensitivity to the drug may be possible as most of the patients affected at first used the drug with impunity with the trouble developing at the next administration. Although the actual mechanism is not known, the rapid onset of the myopia after taking the drug and the apparent recovery after its discontinuance seem to indict sulfanilamide. A good prognosis with no apparent ill after-effects is reassuring.

**Primary Pituitary Adenoma and Cavernous Sinus Syndrome.**—Weinberger and his co-workers state that literature indicates that paralysis of the ocular nerves is not rare in cases of pituitary adenoma but that there is no adequate discussion of its significance when associated with pituitary tumor, the mechanism of its production, the anatomic arrangement which permits it to occur, its diagnostic or prognostic importance or its surgical implications. A study of the 169 cases of pituitary adenoma collected from the Hospital of the University of Pennsylvania disclosed 14 in which paralysis of the ocular nerves dominated the clinical picture and in some comprised the exclusive complaint and neurologic observation. The group,

though showing individual clinical variations, presented a fairly consistent neurologic pattern. The cases are described to draw attention to the effect of pituitary adenoma on the ocular nerves and structures in the cavernous sinus. The cases are divided into groups: Group 1 consists of those in which paralysis of the ocular nerve and trigeminal nerve disturbances were the first and exclusive complaints without impairment of visual function. In group 2 involvement of the structures of the cavernous sinus dominated the clinical picture, although examination disclosed variable degrees of injury to the optic nerves and chiasm. Group 3 cases presented ample evidence of chiasmal injury and the diagnosis of pituitary adenoma was not difficult. The structures contained in the cavernous sinus were involved so that the main clinical symptoms were referred to these structures. Disturbances referable to the ocular and trigeminal nerves played an important role in the symptoms, but evidence of injury to the optic chiasm and optic nerves was compatible with an intrasellar lesion. Although there were many differences among the foregoing cases, there was a basic similarity referable to involvement of the structures in the cavernous sinus. It was shown that occasionally pituitary adenomas grow laterally and that this mode of growth may produce the clinical picture of a lesion in the sphenoid fissure rather than the classic chiasmal syndrome. Radiation seems to relieve the symptoms caused by involvement of the nerves contained in the cavernous sinus. Palsy of the ocular nerves disappeared in 2 cases after roentgen treatment. Surgical extirpation when the tumor has escaped from the sella turcica is difficult and dangerous. Roentgen therapy as a primary treatment for pituitary adenomas should be reconsidered in this light. If roentgen therapy is used first and is unsuccessful, the tumor may spread widely, thus making a surgical attack difficult and hopeless if occasion demands it later on.

### Georgia Medical Association Journal, Atlanta

29:519-562 (Nov.) 1940

- Presentation of the President's Key to Dr. William H. Myers, of Savannah. A. H. Bunce, Atlanta.—p. 519.  
Progress in Knowledge and Control of Cancer. K. M. Lynch, Charleston, S. C.—p. 521.  
Status and Function of the Industrial Physician. L. Noland, Fairfield, Ala.—p. 525.  
Hypometabolism and Myxedema. M. V. B. Teem, Marietta.—p. 528.  
Imperforate Hymen with Hematocolpos: Report of Case. G. A. Holloway, Atlanta.—p. 535.  
Tuberculosis of Bone. H. W. Jernigan, Atlanta.—p. 537.  
A Layman Looks at the Family Doctor. Helen Estes, Gainesville.—p. 540.

### Kansas Medical Society Journal, Topeka

41:453-496 (Nov.) 1940

- The Physician's Responsibility in Industrial Work. E. Wyman, Topeka.—p. 453.  
Ocular Symptoms and Signs in Certain General Diseases. C. S. O'Brien, Iowa City.—p. 456.  
Management of Perforated Appendix. E. R. Gelvin, Concordia.—p. 460.  
Cleidocranial Dysostosis: Survey of Six New Cases and 126 from Literature. P. W. Miles, Kansas City.—p. 462.  
Carcinoma of Cecum Simulating Appendicitis. J. B. Stoll, Clay Center.—p. 468.  
Carcinoma of Fallopian Tube: Report of Two Cases. M. A. Walker and H. H. Hesser, Kansas City.—p. 469.

### Review of Gastroenterology, New York

7:457-550 (Nov.-Dec.) 1940

- Early Experiences in Flexible Gastroscopy. G. McNeer, New York.—p. 457.  
Gastroscopy with Statistical Report of 100 Patients. J. M. Rumball, Pittsburgh.—p. 463.  
Combined Treatment of Gastroduodenal Ulcer. C. A. Brusck and J. A. Brusck, Cambridge, Mass.—p. 471.  
Pain Mechanism in Peptic Ulcer and Pseudo-Ulcer Syndrome: Control of These Disorders with Low Carbohydrate Diet. B. P. Sandler, New York.—p. 485.  
Cooperative and Coordinate Gastroenterologic and Surgical Problems. I. Cohn, New Orleans.—p. 500.  
Chronic Ulcerative Colitis: Deficiency States. I. R. Jankelson and C. W. McClure, Boston.—p. 506.  
Interpretation of Low Metabolism in Gastroenterologic Practice. M. Golub, New York.—p. 512.  
Vitamin K: Its Use in Patients with Obstructive Jaundice or with Biliary Fistulas. H. P. Smith and C. A. Owen, Iowa City.—p. 523.  
Hyperglycemic Shock. C. L. Glaessner, New York.—p. 528.

## FOREIGN

An asterisk (\*) before a title indicates that the article is abstracted below. Single case reports and trials of new drugs are usually omitted.

## British Journal of Surgery, Bristol

28:161-336 (Oct.) 1940

- Carotid Tumors. G. Gordon-Taylor.—p. 163.  
Concerning the Origin and Nature of Certain Malformations of Face, Head and Foot. A. Keith.—p. 175.  
Sacroiliac Tuberculosis. H. J. Seddon and F. G. St. C. Strange.—p. 193.  
Nature and Cause of Swelling of Upper Limb After Radical Mastectomy. E. A. Devenish and W. H. G. Jessop.—p. 222.  
Volkman's Ischemic Contracture. D. L. Griffiths.—p. 239.  
\*Treatment, Complications and Late Results of Acute Hematogenic Osteomyelitis: Based on Study of 500 Cases Admitted to the London Hospital During the Years 1919-1937. E. C. B. Butler.—p. 261.  
Nonmalignant Stricture of Esophagus: Two Cases. G. G. Turner.—p. 275.  
Leiomyomas of Stomach. H. Edwards and E. E. Lewis.—p. 284.  
Spread of Acute Intraperitoneal Effusions. G. A. G. Mitchell.—p. 291.  
Supernumerary and Ectopic Ureters: Carcinoma of Double Kidney, with Ectopia of One Ureter. G. H. Baines.—p. 314.  
Resection of Growths of Lower Pelvic Colon: New Method of Anastomosis. S. Pringle.—p. 320.  
Emphysema of Biliary Passages. P. H. Whitaker and J. P. Steel.—p. 325.

**Acute Hematogenic Osteomyelitis.**—Butler states that acute osteomyelitis is a diminishing disease in the East End of London as, between 1919 and 1928, 344 cases were admitted but from 1929 to 1937 there were only 156 admissions. He attributes this decrease to the better health and home conditions which now prevail; no other cause was evident. There was a higher incidence in males (67 per cent) as compared to females (33 per cent). This is attributed to the more adventurous life and greater exposure to trauma of the male population. The disease was most prevalent up to the age of 20 among both sexes. There was a history of injury in 43 per cent of cases. In no case did osteomyelitis supervene on a simple fracture. A primary septic focus was present in 93 cases. However, the importance of a septic focus was not realized in the past, and its presence or absence was rarely placed on record. More recently a much higher percentage has been found. There were 127 deaths. The rate has been the same for the two sexes. The death rate has remained constant despite the decreased incidence and conservative treatment of recent years. Of the 500 patients, 469 were operated on on admission or shortly after. The death rate of the three main types of operation (drainage of a periosteal abscess, periosteal incision and osseous drilling and drainage of a medullary cavity) were the same, 21 per cent. Immediate amputation saved the lives of 2 patients on whom it was performed, but they both died later from recurrent infections in other bones and pyemia. This suggests that amputation should not be performed until the patient has acquired a real or artificial immunity against the staphylococcus. Twenty-six of the 31 patients who had no operation either had fulminating bacteremia or the diagnosis was made only in the postmortem room. This group accounted for 22 per cent of the deaths. It is unlikely that even early surgery would have benefited them, as the bacteremia was the cause of their deaths. The incidence of sequestrectomy was lowest after drilling the bone. It is reasonable that the lessening of intramedullary tension followed by complete rest in plaster limited osseous destruction. Pathologic dislocation occurred once in the knee and four times in the hip. These late manifestations were not fatal. The fractures united except possibly one which could not be traced. The musculospiral nerves of 4 patients were affected, as were the external popliteal of 2 and the posterior interosseous of 2. All were postoperative lesions. One musculospiral lesion was treated with secondary suture and did well. The external popliteal lesions were permanent; recovery occurred in the others without surgical intervention. There were 124 instances of acute arthritis. Its effect on the immediate prognosis was moderate. However, it did have a bad effect on the ultimate function of the limb. Only 37 per cent of these patients who left the hospital had a movable joint. Of the 500 patients 373 lived and of these it was possible to trace 223; 160 were examined in the follow-up department, 50 answered a questionnaire and 13 had died, giving a late mortality of 3.5 per cent. Of 137 patients observed after ten or more years 121

were at work, 65 had a good result, 58 required recurrent operation, 22 had a recurrent discharge, 32 had recurrent pain and 48 had some deformity. Of 39 patients seen between five and ten years later the respective figures are 36, 20, 18, 8, 7 and 9, and likewise for the 47 admitted during the last four years of the study the figures are 38, 25, 11, 15, 6 and 16. Forty-four of the three groups of patients required operations on other bones, 36, 4 and 4 cases in each respective group. The author's criteria for a good clinical result is a completely healed wound, no deformity of bone or limb apart from a scar and no recent active focus in any part of the body. The surgical treatment of a serious case of osteomyelitis should have the active cooperation of a bacteriologist and a surgeon. The high mortality of this and other acute staphylococcal infections may in this way be reduced eventually.

## British Journal of Tuberculosis, London

34:81-140 (July-Oct.) 1940

- Rounding Out the Tuberculosis Campaign. L. I. Dublin.—p. 84.  
Rehabilitation. P. Varrier-Jones.—p. 91.  
Mental Disturbance in Pulmonary Tuberculosis. R. Y. Keers.—p. 100.  
\*Cod Liver Oil as Local Treatment for Tuberculous Lesions. A. L. Banyai.—p. 107.  
Naturally Occurring Tuberculosis in Dogs and Some Other Species of Animals. R. Lovell and E. G. White.—p. 117.  
Treatment of Tuberculosis of Larynx by Injection. J. R. Roberts.—p. 133.

**Cod Liver Oil Locally for Tuberculous Lesions.**—Banyai reports 164 cases of laryngeal and pharyngeal tuberculosis treated at the Muirdale Sanatorium by the topical application of cod liver oil by spray. Therapeutic effect was studied in 91. All the patients had active pulmonary tuberculosis. The laryngeal lesions were characteristic of tuberculosis associated with a chronic pulmonary process. Relief from disagreeable symptoms was prompt among those patients who responded favorably to the treatment. Several of the ulcer patients who used cocaine spray, anesthesin or euphagin tablets before the treatment were able to discontinue their use shortly after the cod liver oil treatment was begun. The disappearance of dryness, tickling and burning sensation in the throat, the cessation of pain localized to the larynx or radiated to the ear were frequently observed. With the elimination of the pain, dysphagia was relieved and the patient's nutrition and general well-being improved. Also cough diminished and expectoration became easier, permitting more pulmonary and general rest and sleep. Hoarseness disappeared, and the voice was restored to normal. A more optimistic mental attitude on the part of the patient followed these favorable changes. The improvement in the laryngeal lesions was striking as treatment progressed. Ulcers showed a rapid epithelization and healing that was comparable with the results seen in pharyngeal cases, provided the treatment was carried out consistently and well tolerated by the patient. A good therapeutic response was had by patients with various degrees of vegetative granulation. Other manifestations of the disease cleared up also satisfactorily. The patients with marked edema obtained the least effect, with complete failure in several. After treatment was continued from two months to one and a half years the lesions of 24 patients remained unimproved (8 died during the course of treatment), 42 improved subjectively and objectively and the lesions of 25 healed. The tuberculous empyema of 17 patients with no bronchopleural fistulas responded favorably to aspiration of the pus and to its replacement by small amounts of cod liver oil. No local or general reactions were observed. The purulent pleural exudate of 2 patients was reduced to a minimum and thus they became eligible for thoracoplasty for obliterating the infected, gaping pleural cavity. When marked general debility or amyloidosis was present, cod liver oil therapy failed. Cod liver oil aided the formation of healthy granulation, reduced purulent secretion and accelerated epithelization in operative wounds with a delayed tendency to heal. The oil was also of benefit in suppurating tuberculous lymph nodes (when seen early), phlyctenular conjunctivitis, keratoconjunctivitis, cold abscess secondary to bone tuberculosis, fistulas originating from tuberculous epididymitis, ischiorectal fistulas and scrofuloderma.

## British Medical Journal, London

2:619-656 (Nov. 9) 1940

Interpretation of Lateral Radiographs of Chest, with Special Reference to Tuberculosis in Childhood. S. Engel and G. G. Kayne.—p. 619.  
Adsorption of Early Products of Bovine Tubercle Bacilli in Rabbits by Anthracite Dust. S. L. Cummins.—p. 623.  
Convulsive Cardiazol Therapy in Cardiovascular Disorders. R. Good.—p. 624.

\*Benzyl Benzoate Treatment of Scabies. R. E. King.—p. 626.  
One-Layer Operation for Inguinal Hernia. K. Black.—p. 627.

**Benzyl Benzoate Treatment of Scabies.**—Of the many sulfur-free remedies for scabies King found the benzyl benzoate method introduced by Kissmeyer to be the most efficacious. In a series of 100 cases of scabies occurring in a naval establishment, 80 per cent of which were infected and of longer duration than two weeks, treatment by one application of the benzyl benzoate lotion proved completely successful. There were no unpleasant after-effects, except a slight generalized burning sensation, which usually lasted for about fifteen minutes. In 3 cases of gross pyodermitis from scabies infection of long duration the application was repeated after four days because of a recurrence of nocturnal itching. This resulted in the disappearance of all irritation, and the septic cutaneous condition responded to simple treatment. The lotion consists of equal parts of benzyl benzoate, denatured alcohol and soft soap. It is applied vigorously for five minutes with a pig-bristle shaving brush after a thorough scrubbing of the whole body with soft soap and a ten minute soak in a bath at 100 F. After the first application dries another one is applied, the clothes worn before treatment are resumed and twenty-four hours later a bath is taken and clean clothes are put on. The portions of skin showing severe pyogenic infection must be treated as energetically as the unabraded areas.

## Clinical Science, London

4:217-340 (Oct.) 1940

\*Excretion of Pregnanndiol and Corpus Luteum. C. L. Cope.—p. 217.  
Venous Pulsation in Orbit. T. Lewis.—p. 243.  
\*Observations on Periarthritis Nodosa. R. T. Grant.—p. 245.  
Adjustment of Bloodflow to Affected Limb in Arteriovenous Fistula. T. Lewis.—p. 277.  
Pituitary-like Factors in Blood and Urine of Diabetic Patients and of Animals Treated with Pituitary Extracts. H. P. Himsworth and R. B. Kerr.—p. 287.  
Somatic Stimulating Visceral Pain. J. H. Kellgren.—p. 303.  
Simplification of Evans Blue Method of Blood Volume Determination. C. R. Harington, E. E. Pochin and J. R. Squire.—p. 311.  
Thyrotropic Hormone in Blood. H. B. Collard, F. H. Mills, F. F. Rundle and E. P. Sharpey-Schafer.—p. 323.  
Instrument for Measuring Quantity of Blood and Its Degree of Oxygenation in Web of Hand. J. R. Squire.—p. 331.

**Excretion of Pregnanndiol and Corpus Luteum.**—Cope presents clinical material which confirms the principal claims of Venning and Browne that pregnanndiol is excreted in the urine only during corpus luteum activity. Excision of the corpus luteum during early pregnancy results in a rapid fall to zero of the pregnanndiol excretion, which normally continues in increasing amounts to full term. Pregnanndiol is excreted during the luteal phase of the menstrual cycle, falls to zero before bleeding commences and is absent from the urine during the first or preovulatory half of the cycle. In contrast to this, no such excretion of pregnanndiol occurred over a period of several weeks in two women suffering from secondary amenorrhea in whom it was unlikely that ovulation was occurring. No pregnanndiol was excreted during three excessive uterine bleedings of a woman with a diagnosis of nonovulatory bleeding. This provides additional evidence of the close association between corpus luteum activity and pregnanndiol excretion. All this is compatible with the main thesis of Venning and Browne. It must be remembered, however, that activity of a corpus luteum in nonpregnant women is usually associated with a secretory type of endometrium. The fact that the corpus luteum of pregnancy may be removed at the second or even the first month without abortion has led to the assumption that under these conditions the chorionic villi take over the hormone producing function of the corpus luteum. Since this seems very probable, the author feels that the adoption of a similar endocrine function by the normal premenstrual secretory endometrium is not an impossibility. Injection of progesterone to women not excreting any pregnanndiol caused a small but

definite amount of the substance to appear in the urine. In view of this it is not justifiable to assume that the magnitude of pregnanndiol excretion necessarily gives any quantitative indication of the rate of progesterone production by the corpus luteum. The state of the endometrium might prove an important factor in determining the percentage yield of pregnanndiol from a given quantity of progesterone. However, pregnanndiol excretion curves may reflect the state of the endometrium more closely than the activity of the corpus luteum. Until contrary evidence is had, it must be assumed that the observed pregnanndiol excretion represents only a small proportion of the total endogenous progesterone production. Therefore it must be determined whether pregnanndiol is the most important excretory product of endogenous progesterone. Available evidence does not reveal appreciable quantities of any substance in the urine other than pregnanndiol glucuronide and allopregnanndiol, probably also present as a glucuronide, which might be considered a breakdown product of progesterone metabolism. The author concludes that pregnanndiol excretion is a qualitative indication of corpus luteum activity in the nonpregnant woman and that it probably indicates progesterone production in pregnant and nonpregnant women. He does not believe that the pregnanndiol excretion rate provides any reliable estimate of the intensity of corpus luteum metabolism. The great discrepancy between the relatively large amounts of pregnanndiol recovered after progesterone injection by Venning and Browne and the failure to recover any by Hamblen, Ashley and Baptist and by Stover and Pratt together with the author's intermediate recoveries suggests to him that other factors, at present undefined, are concerned in determining the pregnanndiol excretion from a given quantity of progesterone. If this is probable after injected progesterone it may be equally probable for endogenous progesterone. He believes that hormone influences other than renal or hepatic and the metabolic state of the uterus and endometrium will prove to be important in progesterone metabolism and pregnanndiol excretion. The assumption that pregnanndiol excretion reflects quantitative variations in corpus luteum activity is unsupported by direct evidence.

**Periarthritis Nodosa.**—Grant reports 7 cases of periarthritis or polyarthritis nodosa and suggests that the condition is much less rare than is commonly thought, that it is not necessarily or even usually fatal and that it can be recognized at the bedside in a considerable proportion of cases. Of his 7 patients encountered since 1937 only 3 have died. The diagnosis was made on clinical grounds and confirmed microscopically in 4, in 2 others it was suspected during life and in 1 it was discovered after death. Unfamiliarity with the disease may account for some of its assumed rarity. Familiarity with its general features reveals many cases that present a complex combination or succession of symptoms that sooner or later suggest the diagnosis.

## Indian Medical Gazette, Calcutta

75:513-576 (Sept.) 1940

Taking Blood for Transfusion (in Potain's Aspirator): Further Details Including Cold Storage. S. D. S. Greval, S. N. Chandra and A. B. Roy Chowdhury.—p. 513.  
Buffer Precipitation Test for Malaria (B. P. T.) Adjusted for Large Scale Examinations. E. K. Wolff.—p. 517.  
Observations on Differentiation of Bacterium Coli and Bacterium Aerogenes on Levine's Simplified Eosin Methylene Blue Agar as Applied to Bacteriology of Water in Bengal. S. Neogi.—p. 519.  
Vibrio Cholerae and Other Vibrios: Observations on "Water Vibrios" with Special Reference to Their Variation During Storage in Culture Medium and Possible Relationship to Vibrio Cholerae. A. C. Vardon.—p. 522.  
Modern Concept of Uremia and Its Clinical Study: Based on Series of 44 Cases. M. N. De and J. C. Banerjee.—p. 527.

## Journal of Laryngology and Otology, London

55:405-448 (Sept.) 1940

New Tests and Clinical Experiments on Hearing. F. W. Kohrak.—p. 405.

## South African Medical Journal, Cape Town

14:391-410 (Oct. 26) 1940

The Problem of Asthma. N. V. Storr.—p. 393.  
Cholecystitis and Its Diagnosis. C. D. Brink.—p. 397.  
New Operation for Inoperable Vesicovaginal Fistula. A. B. Taylor.—p. 401.



**Presse Médicale, Paris**  
**48:689-704 (Sept. 4-7) 1940**

- \*Bilateral Supradiaphragmatic Splanchnicectomy in Surgical Treatment of Arterial Hypertension. P. Wertheimer.—p. 689.  
Modification of Induced Hyperglycemia by Ingestion of Fats. F. Sciclounoff and E. Martin.—p. 691.  
Grave Paralysis in Course of Cerebrospinal Meningitis (Six Cases): Dangers Inherent in Intraspinal Injections of Sulfapyridine. P. Fort and M. Igert.—p. 693.  
Value of Bromide Therapy, Single or Combined in Intravenous Administration. A. Landau.—p. 695.

**Supradiaphragmatic Splanchnicectomy in Arterial Hypertension.**—Wertheimer discusses bilateral splanchnicectomy by way of the posterior mediastinum based on 5 patients with arterial hypertension. Four of the 5 patients (aged 35, 43, 56 and 58 years, only one giving a familial history) had headache, vertigo, precordial pain and visual and nervous disorders associated with varying degrees of high blood pressure. The operation, which is described, succeeded in suppressing all subjective manifestations though it did not restore blood pressure to normal levels. Of 1 patient (aged 35 years) the arterial tension six months later was seen to be 175 mm. systolic and 125 mm. diastolic, though improved from the earlier 215 mm. systolic and 140 mm. diastolic gage; 2 others (1 aged 56) had subjective improvement which persisted though blood pressure levels were no lower. Splanchnicectomy, according to the author, is contraindicated for persons past 50, in renal lesions with significant urea retention and albuminuria and in cardiac involvements. Surgical intervention in persons older than 50 years needs to be supported by weighty considerations. Bilateral supradiaphragmatic splanchnicectomy, done in a single intervention, suppresses angiospastic states due to renal ischemia. It does not guarantee permanent vasodilatation in the splanchnic area but sets up a resistance to abnormal vasoconstriction. The author believes that the operation is not to be regarded as a therapeutic measure of last resort but one the applicability of which should be considered for patients past 50 who show a high diastolic pressure, a systolic pressure around 200, hypertensive retinitis, a somewhat enlarged cardiac shadow, a dilated heart responsive to digitalis and so on. He believes that a striking analogy exists between arterial hypertension with vascular neurotonia affecting the renal system and Raynaud's disease with vascular neurotonia disturbing the peripheral circulation.

**48:721-736 (Sept. 17) 1940**

- \*Possibility of a New Surgical Procedure for the Treatment of Definitive Facial Paralysis. R. Leriche.—p. 721.  
Primary Tuberculous Infection and Exogenous Reinfection. E. Rist.—p. 722.

**Surgery for Facial Paralysis.**—Leriche proposes anastomosis between the sympathetic and the facial nerve for relief of facial paralysis. Twenty years ago his proposal to alleviate permanent lagophthalmos by section of the cervical sympathetic was favorably received and led to successful results at the hands of other surgeons. Admittedly a palliative operation, improvement was further sought by means of hypoglossal and spinal anastomosis, but without truly satisfactory results. Leriche now has come to believe that anastomosis can be combined with the section of the sympathetic in a simple operative procedure in which the sympathetic trunk is sutured end to end with the facial nerve. In this way the immediate advantages of sympathetic section could be combined with those of subsequent regeneration. Heterogenic regeneration thus envisaged finds support in the work of other investigators who found that the sympathetic can be neurotized by the vagus, the hypoglossal and nerves belonging to the spinal nervous system. The possibility that the sympathetic would admit of neurotization by nerves belonging to the cerebrospinal system was indicated by animal experiments of Ballance and his associates. Anastomosis of the central termination of the cervical sympathetic with the peripheral end of the facial nerve made possible the transmission of nerve impulses of cerebral origin to the periphery. Experiments on cats indicated that the sympathetic lent itself to neurotization by somatic nerves such as the facial. Ballance did not apply the results of these experiments to man. He propounded as the method of choice for facial paralysis fresh nerve grafting in the facial canal, which he found successful in experiments on two monkeys. Leriche is of the opinion that anastomosis between sympathetic and facial nerve by virtue of its surgical simplicity offers a better surgical solution.

**Anales de Cirugía, Rosario****6:223-339 (Sept.) 1940. Partial Index**

- \*Anthrax of the Kidney: Clinical Study. R. Ercole and A. Fort.—p. 263.  
Treatment of Old Fractures of Neck of Femur by Subtrochanteric Osteotomy. O. R. Marótti.—p. 298.

**Anthrax of Kidney.**—Ercole and Fort call attention to the importance of pyelography in the diagnosis of renal anthrax. They report 4 cases in which the preoperative diagnosis was made by pyelography. Renal anthrax is more frequent than is believed. It frequently causes perirenal abscess and may pass unobserved unless pyelography is systematically practiced in the presence of such an abscess. The patients give a history of suppuration in regions remote from the kidney, such as furuncles and felons, one or two months before the appearance of renal symptoms. Pain in the lumbar region and symptoms of general infection predominate over those of the perirenal abscess in some of the cases. The urine does not contain pus cells. The diagnosis is arrived at by pyelography, which reveals the tumor or abnormalities in the renal pelvis and renal calices or displacement of the structures by compression. The treatment consists in either partial or complete nephrectomy or enucleation of the tumor. Nephrectomy is indicated when the tumor occupies a considerable portion of the renal parenchyma or is situated centrally. In the cases reported by the authors the preoperative diagnosis was confirmed by macroscopic and microscopic studies of the kidney removed by nephrectomy. Recovery took place in all cases.

**Clinica Ostetrica e Ginecologica, Rome****42:473-520 (Oct.) 1940. Partial Index**

- \*Diagnosis of Rupture of Amnion. A. La Delfa.—p. 473.  
Malignant Granuloma in Pregnancy. A. de Palo.—p. 477.

**Diagnosis of Rupture of Amnion.**—According to La Delfa there are cases of dystocia in which cesarean section is indicated and in which diagnosis of rupture of the bag of waters is necessary and difficult. Results of tests based on variations of the pH of the vaginal secretion are not reliable. La Delfa investigated the diagnostic value of von Numer's test (See *Acta obstetrica et gynecologica Scandinavica* 16:249, 1936). The test is based on the occurrence in the vaginal secretion of free drops of fat or cells of fetal sebaceous glands derived from vernix caseosa. A drop of vaginal secretion is taken from the vagina with a platinum loop and is spread on a slide carefully defatted. The slide is air dried without previous fixation, stained at room temperature in a solution of 0.2 or 0.3 Gm. of sudan III in 100 cc. of 70 per cent alcohol, washed in water, dried with blotting paper and immediately examined with low magnifying power. Fetal fat substances are stained a distinct orange red. They must be differentiated from particles of mucus and fat droplets of vaginal epithelial cells, which stain a faint yellowish pink. Abundance of fat particles in the vaginal secretion justifies the presumption that rupture of the membranes has taken place. Negative sudan reaction speaks for the reverse. In a series of 160 cases reported by the author, the test was negative in a group of 50 pregnant women at full term and in a group of 62 women at labor with intact bag of waters. The test was positive in a group of 35 women in labor shortly after the rupture of the membranes and during the first twenty-four hours after the rupture and in 12 of 13 women twenty-four or forty-eight hours after the rupture. When positive, the test is an absolute proof of rupture of the membranes.

**Deutsche medizinische Wochenschrift, Leipzig****66:337-364 (March 29) 1940. Partial Index**

- Prophylactic Treatment of Gas Edema After Gunshot Injuries. N. Guleke.—p. 337.  
\*Present Status of Control of Anaerobic Wound Infections. J. Zeissler.—p. 340.  
Surgical Experiences in the Polish War. H. Wildegans.—p. 343.  
Amputation of Limbs. H. Bürkle-de la Camp.—p. 347.  
Value of Tomography for Localization of Foreign Bodies. W. Kremer.—p. 351.  
Gas Gangrene. M. Westenhöfer.—p. 353.  
Results of German War Surgery in Past Centuries. W. von Brunn.—p. 353.

**Anaerobic Wound Infections.**—According to Zeissler the most feared wound infections during war are tetanus, gas gangrene and malignant edema. Gas edema is a collective term for gas gangrene and malignant edema, which frequently

develop as mixed infections. The majority of gas edemas, particularly gas gangrene, are produced by *Clostridium welchii* (B. perfringens). The next most frequent gas edema organism is Novy's bacillus of malignant edema (B. oedematiens) and still another is the *Vibrio septique*. These bacilli were known before 1895. Since that time the following gas edema bacilli have been discovered during and after the World War: *Bacillus histolyticus*, *Bacillus oedematis sporogenes*, *Bacillus haemolyticus*, *Bacillus gigas* and three organisms that are only toxicologically differentiable from *Bacillus welchii*, namely *Bacillus agni*, *Bacillus ovitoxicus* and *Bacillus paludis*. The latter three have never been observed in human subjects. The *Rauschbrand bacillus* (B. chauvaui) was discovered in 1881. The knowledge regarding gas edema is far in advance over what was known at the beginning of the World War. Not only are the organisms known which cause it, but also the frequency of their occurrence in the soil of different battle fields. Gas edema serum is a valuable adjuvant to the surgical treatment of gas edema. The fact that the time elapsing between the injury and the outbreak of the gas edema is usually short makes quick action important. This action consists in a thorough surgical cleansing of the wound which removes all foreign bodies, dirt and necrotic and nonviable tissues and, if necessary, of administering specific antitoxins in the form of serum. In view of the short incubation period and the rapid course of gas edema, small doses of serum are inadequate for prophylaxis as well as for treatment. Recent investigators, among them Löhr and Konjetzny, administer from 300 to 500 cc. of gas edema serum, chiefly by means of the intravenous drip. The gas edema serum contains antitoxins against the most important gas edema bacilli: (1) *Bacillus welchii*, (2) Novy's bacillus of malignant edema (B. oedematiens), (3) *Vibrio septique*, (4) *Bacillus histolyticus*. In view of the fact that large quantities of gas edema serum are required for effective action, its administration should be limited to the cases in which either gas edema has already developed or in which the severity of the wound or the local frequency of gas edema make serotherapy advisable. The author maintains that local chemotherapy is ineffective and warns against the injection of chemicals in the surroundings of the wound. Such injections may cause trophic disturbances in the tissues or even tissue necroses and thus provide one of the factors favoring the development of gas edema.

#### 66:393-420 (April 12) 1940. Partial Index

- Metabolic Experiments on Protein Supply of German People During Winter of 1939 to 1940. A. Bickel.—p. 393.  
 \*Prophylaxis of Scarlet Fever. W. Schultz.—p. 396.  
 \*Control of Fatigue by Autogenous Active Substances. T. Morell.—p. 398.  
 Chemotherapy for Reduction of Treatment Time in New Gonorrhea. Lindemann, Felke and Schleich.—p. 401.  
 Origin and Development of Nonpigmented Forms of Malaria Parasites. W. Schulemann and K. Spies.—p. 404.  
 Utilization of Mushrooms. E. Nossel.—p. 405.  
 Studies on Chemotherapy of Tuberculosis. E. Hesse and Gertrud Meissner.—p. 407.

**Prophylaxis of Scarlet Fever.**—Schultz places especial emphasis on a sufficiently prolonged isolation in the prophylaxis of scarlet fever. The biologic prophylaxis is accomplished at his clinic chiefly with human serum. The efficacy of horse immune serum is established, but its extensive application for prophylactic purposes is inadvisable because, in addition to possible immediate complications, there is danger that later administration of horse serum (tetanus antitoxin and so on) may provoke severe reactions. It is likewise probable that the protective action of the serum rapidly diminishes. In view of these disadvantages of horse serum in the prophylaxis of scarlet fever, passive immunization with convalescent serum has been recommended. This serum is obtained between the fourth and the sixth week of the disease. Because collection of convalescent serum involves difficulties, attempts have been made to utilize serum of adults. It has been proved by Wiecke and others that, with increasing age, persons become more and more immune to scarlet fever, even though they have not had the disease, and that the serum of adults of comparatively advanced age (40 and up) is more effective than the convalescent serum. The author is unable to explain this immunobiologic phenomenon but accepts it as a fact, the more so since normal human serum is also of

therapeutic value. In a number of cases in which scarlet fever was anticipated, the author administered 10 or 20 cc. of serum from adults with the result that scarlet fever did not develop. He admits, however, that this is not a definite proof of the prophylactic value of the serum. The active method of immunization has been used less extensively. It employs a scarlet fever vaccine which, in addition to killed scarlet fever streptococci, contains an anatoxin. This vaccine, however, may cause a general reaction in sensitive persons. Combination of passive and active immunization is also possible. The use of serum from adults makes the problem of biologic prophylaxis of scarlet fever much less complicated than it was formerly. The serum is obtained from patients who have hypertension, polycythemia and other conditions and who are free from infectious disease. Serum is stored in an icebox. Observation of necessary precautions obviates harmful effects.

**Control of Fatigue by Active Substances.**—The problem of fatigue demands particular attention at the present time, according to Morell. Fatigue reduces performance. The problem becomes urgent in aviators who have to fly at high altitudes where they have to resort to oxygen respiration. The cold and prolonged exposure to the noise of the motor increase the fatigue beyond physiologic endurance. The reaction capacity becomes greatly decreased. Means for removal and detoxication of fatigue substances are therefore much to be desired. If the performance capacity is to be increased, it is advisable to supply the organism by way of food with sufficient biocatalytic agents and with energy producing substances. Not only must they be supplied in adequate quantities, but physiologic proportioning is important. The author mentions vitamin C and B complex as important activators and dextrose as an important foodstuff molecule. The proper caloric utilization of dextrose is possible only in the presence of physiologically adequate amounts of vitamins B and C. The author reviews the mode of action of these vitamins and describes work test experiments in the course of which he studied the effect of a preparation containing dextrose and vitamins B and C. He found that performance increases greatly if the preparation is given during extreme fatigue. He recommends its use in the course of exertion.

#### 66:729-756 (July 5) 1940. Partial Index

- Treatment of Open Fracture of Cranial Vault. F. Heck.—p. 731.  
 Treatment of Febrile Mastitis During Puerperium with Special Consideration of Use of Short Waves. H. Jacobi.—p. 734.  
 Therapeutic Use of Thionine in Dextrose in Anoxia: Foundations of This Therapy. W. Herbrand and K.-H. Jaeger.—p. 736.  
 \*Intrasternal Injection and Transfusion as Substitute for Intravenous Methods. N. Henning.—p. 737.  
 Treatment of Dermatoses During War. Mohrmann.—p. 739.

**Intrasternal Injection and Transfusion.**—Henning found in a number of experiments that substances injected into the spongiosa or medullary cavity of the sternum find their way quickly into the blood stream by way of the internal mammary vein. He investigated the question of substituting intrasternal injection or transfusion for intravenous injection or transfusion. He found that sternal injections of strophanthin, of hypertonic solutions of sugar or of sodium chloride and of other intravenously administered medicaments are tolerated without reactions and that it is possible to give blood transfusions in this manner. After puncture, an irrigator containing blood is attached and the blood is allowed to run in from an elevation of 1 meter. The inflow velocity is slightly less than in the case of intravenous transfusion. The inflow may be made faster by attaching two needles to the tube. Sternal injection or transfusion is indicated in cases in which it is difficult to find veins in the extremities, or in vascular collapse which no longer permits adequate filling of the veins. It should be valuable under war conditions, when an intravenous injection or a blood transfusion becomes necessary during collapse, after severe injuries or great loss of blood. The sternal transfusion has the advantage that the cannula requires no particular attention, because it stands fixed in the compact mass. The technic of sternal puncture is so simple that it involves no difficulties. The author makes the puncture in the midline of the third, fourth or fifth intercostal space. He uses local anesthesia for the skin, subcutis and periosteum and, since the periosteum is extremely sensitive, he places several small subperiosteal depots of procaine hydro-

chloride. After the needle has reached the external compacta, several turning movements are made to penetrate it. The instrument is fixed with the left hand in order to prevent a sudden deep penetration.

#### 66:785-812 (July 19) 1940. Partial Index

- \*Present Status of Knowledge on Etiology and Epidemiology of Hodgkin's Lymphogranulomatosis. P. Uhlenhuth and K. Wurm.—p. 785.  
Therapeutic Results in Brain Tumors by Roentgen Irradiations of Closed Cranium. Lucie Rüksen-Brosowski.—p. 790.  
Paralyzing Effect of Opiates on Respiratory Function. F. Eichholtz.—p. 792.  
Possibility of Selective Heating of Some Tissue Layers in Ultra-Short Wave Condenser Field. E. Hasché.—p. 797.  
Periproctitic Abscesses and Anal Fistulas. P. Rostock.—p. 800.

**Etiology of Hodgkin's Lymphogranulomatosis.**—Uhlenhuth and Wurm review the present status of the etiology and epidemiology of Hodgkin's lymphogranulomatosis. They submit the results of studies carried on over a period of several years in collaboration with clinics as well as reports from the literature. They had investigated the question of Hodgkin's disease being infectious. This theory has found wide acceptance because of the clinical course, the anatomic character of the lesions and certain epidemiologic aspects. Various types of micro-organisms have been demonstrated in the excretions, the blood, the glands and the organs of patients with Hodgkin's disease and have been suggested as causal organisms. The most stubbornly defended theory was that of tuberculous etiology, first suggested by Sternberg in 1898. This problem was studied in 70 cases. The bacterioscopic demonstration of tubercle bacilli with the Ziehl-Neelsen method and with methods to bring about abundant growth of the organism has invariably failed. The guinea pig test was positive in 3 of 33 cases. In 1 of the 3 cases necropsy revealed that active generalized tuberculosis coexisted with Hodgkin's disease. Because of L'Esperance's claim that the *typus gallinaceus* of the tubercle bacillus is the causal agent they inoculated chickens with material from patients with Hodgkin's disease, but none of the chickens contracted tuberculosis. They admit that many problems of the relationship between Hodgkin's disease and tuberculosis require further clarification, but on the basis of the available evidence the etiology of Hodgkin's disease has no relation to tuberculosis because (1) the demonstration of tubercle bacilli in Hodgkin's disease is not frequent enough, (2) Hodgkin's disease differs immunobiologically from all forms of tuberculosis, (3) roentgenotherapy is well tolerated in Hodgkin's disease and poorly in tuberculosis, (4) there is no form of tuberculosis which is as fatal as Hodgkin's disease, (5) the local differentiation of the lesions in case of existence of the two contraindicates identical etiology, (6) if Hodgkin's disease had a tuberculous etiology it should be possible to produce it in the animal experiment. In connection with the virus theory the authors direct attention to Gordon's test, which while diagnostically valuable, is not specific. The virus theory has not been demonstrated. Although an increasing number of investigators classify Hodgkin's disease with neoplastic diseases, sufficient proof for it does not exist. According to some statistics the deaths from Hodgkin's disease amount to about 120 per 10,000,000 people annually. The geographic distribution varies. In some countries an increase has been observed in recent years. The authors doubt the higher incidence in the age group between 20 and 40 but cite a large statistical material from the United States, which indicates that the disease increases with age. The same material also proves the higher incidence in men than in women (100 men to 57 women).

#### 66:813-840 (July 26) 1940. Partial Index

- Experimental Foundation of Headache Therapy. G. Schimert Jr.—p. 813.  
Glossopharyngeal and Trigeminal Neuralgia and Its Treatment with Snake Venom. W. Behrmann.—p. 817.  
Physical Therapy in After-Treatment of War Injured. H. Adam.—p. 819.  
Balneotherapy of Members with Impaired Movement and of Poorly Healing Wounds. K. Schnelle.—p. 821.  
Osteogenic Brain Abscess and Its Treatment. A. Herrmann.—p. 824.  
Is Rechterew's Disease a Spondylarthritis? E. Guntz.—p. 826.  
Azosulfamide in Therapy of Anthrax. J. Dörfel.—p. 827.

**Snake Venom in Neuralgia.**—Behrmann knows of no systematic investigations on the use of snake venom in the treatment of neuralgias in the region of the face and head. He reports 3 cases of his own in which he resorted to this treat-

ment. The first patient, a woman aged 54, for five months had suffered from severe pains in the tongue. Lightning-like extreme pains were felt first after eating and later when opening the mouth or speaking. Several weeks later, peculiar taste sensations were experienced. The swallowing of dry foods became painful and later impossible. Treatment with various analgesics and with nonspecific vaccine therapy was ineffective. Snake venom in the amount of 0.25 cc. was injected deep into the muscle. This was increased after an interval of three days to 0.5, and later to 1 cc. Injections of 1 cc. of the venom were administered once or twice weekly. After three weeks of treatment the patient was entirely free from pain and her general appearance was greatly improved. She gained in weight and has remained free from pain for over a year. The second patient had trigeminal neuralgia. Ten injections of snake venom produced complete freedom from pain. In the third patient with trigeminal neuralgia the effect of venom therapy was not so favorable. This woman, however, had leontiasis ossea, and the anatomic changes in the cranial bones were responsible for the neuralgia. In the other two there existed general and cerebral arteriosclerosis. Arteriosclerotic neuritis is especially likely to develop in the trigeminal nerve because its root area has few vessels and is exposed to pontile circulatory disturbances. Snake venom in addition to the analgesic effect possesses cytolytic and proteolytic effects on the vascular endothelium. It reduces blood pressure, produces a more favorable circulatory state, increases the metabolism of the nerves and counteracts the neuralgic pain.

#### Geburtshilfe und Frauenheilkunde, Leipzig

2:387-440 (Aug.) 1940

- Question of Correctness of Concept of Primacy of Ovum. L. Seitz.—p. 387.  
\*Prognosis and Possibilities of Modern Therapy of Febrile Abortion. W. Benthin.—p. 393.  
Therapy of Early Puerperal Mastitis: Local Application of Synthetic Estrogenic Substances. E. Leinzinger and R. Bayer.—p. 414.  
Inversion of Uterus Developing in Connection with Labor or as Sequel of Tumors. A. Ebergényi.—p. 425.  
Late Results of Therapy of Amenorrhea by Means of Intraovarian Injections of Hormone Preparations. C. Stancu.—p. 433.

#### 2:441-494 (Sept.) 1940. Partial Index

- \*Prognosis and Possibilities of Modern Therapy of Febrile Abortion. W. Benthin.—p. 444.  
Fat Tissue Flaps from Bulbocavernous Region as Protective Plastic Operation in Sutures of Fistulas. H. Martius.—p. 453.  
Relapse in Endometriosis. F. Movers.—p. 460.  
Giant Ovarian Cysts. L. Lajos.—p. 475.

**Prognosis and Therapy of Febrile Abortion.**—According to Benthin, complications are to be anticipated in approximately 15 per cent of febrile abortions. The mortality rate is 7 per cent, much higher than in febrile puerperal states. Of patients with para-uterine infections at the time of hospitalization, 31 per cent die. A considerable number remain sterile and those with primary recovery may develop later sequels. Expectant treatment offers best results in cases in which infection is confined to the uterus. Spontaneous expulsion takes place under expectant treatment in from one sixth to one third of the cases. Quinine and ergotamine tartrate promote the expulsive efforts, especially if employed with vaginal tamponade. This tamponade stimulates uterine contractions and prevents excessive loss of blood. The use of carbon and of the ice bag are valuable in restricting the infectious process to the uterine cavity. Early medication with sulfanilamide is advisable for the prevention and arrest of general septic infections and in peritonitis. The expectant treatment requires strict bed rest. A well planned expectant treatment prevents sepsis and pyemia and para-uterine infections. The operative evacuation of the uterus can be tried without much danger five days after the fever has subsided. An earlier or immediate surgical evacuation is permissible only in extremely urgent cases. There exists no vital indication for operative evacuation as long as the cervical canal is still closed. This should be kept in mind especially in the presence of parametritis, peritonitis and inflammations of the adnexa. If the cervical canal is open and if severe hemorrhage exists, interventions are permissible and, if placental parts are already undergoing expulsion, their removal is indicated.

The digital method is the most reliable and least harmful. It should be performed in deep anesthesia and as carefully as possible. Introduction of carbon into the evacuated uterus promotes detoxication and rapid discharge of secretions. Azosulfamide, dextrose, continuous infusions, administration of vitamins and blood transfusion are the most important aids in the treatment of infection. All febrile abortions should be treated in a hospital.

### Medizinische Klinik, Berlin

36:699-730 (June 28) 1940. Partial Index

Protection of Those in Danger of Psychopathic Development. J. H. Schultz.—p. 699.

Prophylactic Surgical Wound Therapy at the Front. G. Schöne.—p. 703.

Prophylaxis and Treatment of War Epidemics (Dysentery, Typhoid, Influenza). H. Löhr.—p. 705.

\*Nonsurgical Treatment of Thyrotoxicoses. H. Wiebel.—p. 707.

\*Symptomatology of Coronary Thrombosis. R. Bürklen.—p. 709.

Pathogenesis of Tetanus. H. zur Horst Meyer.—p. 711.

Prevention of Dental Caries. H. Goll.—p. 712.

**Nonsurgical Treatment of Thyrotoxicosis.**—According to Wiebel, thyrotoxicosis is mainly a disease of women (3:1) particularly common during the years when family and occupation make the greatest demands. Although disturbances in the correlation between the sympathetic nervous system and secretory glands play an important part in the pathogenesis of the disease, the problems of life and environment undoubtedly contribute much. One of the most important features of the internal treatment is to change these conditions by hospitalizing the patient. Internal treatment including roentgen therapy, should be tried in the mild and in some moderately severe cases of thyrotoxicosis. Therapy with phosphorus and arsenic preparations, various diets, iodine, fluorine, vitamin A, injection of animal blood and roentgen rays is reviewed. Observations made in over 400 cases treated at the author's clinic in the course of the last two years indicate that no internal treatment offers permanent results in the severe and in most of the moderately severe cases of thyrotoxicosis. The author regards surgical treatment as the method of choice in all severe and moderately severe cases of thyrotoxicosis.

**Symptomatology of Coronary Thrombosis.**—Bürklen describes a new symptom which he thinks may be of value to the general practitioner. He has demonstrated that in patients with coronary thrombosis with subsequent myomalacia cordis the temperature may differ in the two axillae. This difference, which may amount to as much as 1.2 degrees C. (2.16 degrees F.), is due to the vasoconstrictive irritation originating in the diseased portion of the coronary artery. The temperature is lower in the axilla of the diseased side. Thus, if a branch of the left coronary artery is obstructed, the temperature will be lower in the left axilla. This behavior of the axillary temperature results only from coronary occlusion. The symptom is of differential diagnostic value in thoracic diseases, particularly in pneumonia and in pleurisy, two disorders which are especially difficult to differentiate from coronary thrombosis.

36:763-794 (July 12) 1940. Partial Index

Care of the Eyes of Soldiers in the Field. W. Gilbert.—p. 763.

What Can Be Expected from Protective Inoculation Against Typhoid and What Preparations and Methods Are to Be Recommended? M. Gundel.—p. 764.

Achylic Nervous Disorders. K. W. Essen.—p. 766.

\*Teschen Paralysis of Hogs and Possible Relationship to Disorders of Central Nervous System in Human Subjects: Importance of Cooperation Between Physician and Veterinary. A. Kment.—p. 769.

Infectious Chorea Minor: Diagnosis, Cause and Treatment. H. Stefan.—p. 770.

Treatment of Epidemic Meningitis. E. Türk.—p. 774.

Regulation of Evacuation of Bowels. W. Kaufmann.—p. 775.

**Paralysis of Hogs and Central Nervous System Disorders in Man.**—According to Kment, since 1929 an infectious paralysis has been observed among hogs which is referred to as Teschen paralysis, because it appeared first in a locality named Teschen. The causative agent is an ultraviable, filtrable, neurotropic virus. The disease has been named "encephalomyelitis non purulenta enzootica suum." The paralysis affects particularly the posterior extremities but may involve the anterior ones as well. If the animals do not die of respiratory paralysis early in the disease, the disorder may persist for months. The animals usually have fever. The symptomatology

and the microscopic appearances of the central nervous system recall human poliomyelitis. The author admits, however, that similarity in the microscopic picture does not establish identity of the disease. It has not so far been transmitted to human beings, and injections into monkeys were not successful. Many problems connected with this hog paralysis are still unsolved, but the author suggests that Frauchiger's observations on poliomyelitis in a heifer and in hogs (see *THE JOURNAL*, July 2, 1938, p. 74 and *Schweiz. med. Wchnschr.* 69:71 [Jan. 28] 1939; abstr. *THE JOURNAL*, March 25, 1939, p. 1202) are of interest in this connection. He thinks that the disease which Frauchiger observed was Teschen paralysis, a disease which until then had never been observed in Switzerland. A connection may exist between this paralysis in hogs and the "maladie des jeunes porches" (disease of young swineherds) which has been observed in the Swiss-French border region (see *Schweiz. med. Wchnschr.* 67:709 [July 31] 1937; abstr. *THE JOURNAL*, Sept. 25, 1937, p. 1083) and which is a form of serous meningitis, possibly an abortive form of poliomyelitis. There is no proof of identity of the Teschen paralysis of hogs and of poliomyelitis, although the similarity of the symptoms of the two diseases is striking.

### Münchener medizinische Wochenschrift, Munich

87:877-904 (Aug. 16) 1940. Partial Index

\*Chief Problems of Bright's Disease. F. Volhard.—p. 877.

Surprising Blood Picture in Old People. K. Bürker.—p. 882.

Sex, Age and Occupational Distribution in Ventricular and Duodenal Ulcer. A. Weidinger.—p. 882.

Prevention and Treatment of Soreness of Nipples During Nursing Period. A. Poerschke.—p. 885.

Experiences with Calcium-Bromine Therapy in Dermatology and Venereology. O. Schuester.—p. 886.

Economics in Staining of Gonococci and Spirochetes. H. Lipp.—p. 888.

**Bright's Disease.**—According to Volhard the problems presented by Bright's disease concern chiefly its pathogenesis. He poses the question of the bilateral hematogenic or internal renal disease as contrasted with the urologic or surgical diseases of the kidney, as involving practically the entire organism: the brain, eye, skin, circulation, heart, arteries, blood and lymph capillaries, blood, bone marrow, water exchange, acid-base equilibrium and the metabolism. Three factors are of importance in this connection: (1) the decrease in the secretory activity of the kidney, (2) the increase in the permeability of the renal membranes, particularly of the glomeruli, and (3) the disturbed blood perfusion of the glomeruli. Until recently nearly all remote symptoms of kidney disease were ascribed to failure of its secretory function. The introduction of the water and concentration tests has made it possible to investigate which of the numerous remote effects occur with and which occur without the disturbance of the renal function. It was found that the most striking symptoms, such as dropsy, hypertension, albuminuric retinitis and convulsive uremia, occur also in the absence of renal insufficiency. This raised the question as to the part renal insufficiency plays in the disease. Renal insufficiency is due to a decrease in the number of secretory elements manifested in the qualitative change in the secretory function which begins with a reduction in the concentration capacity and compensatory polyuria, which passes into isosthenuria and pseudonormaluria; that is, secretion of a blood isotonic urine of the specific gravity of deproteinized blood in reduced quantities. If in the presence of isosthenuria the quantity of urine sinks below 1 liter, the condition is irrevocable. The clinical picture of absolute renal insufficiency, true uremia, is that of intoxication. There is a shifting of the acid-base balance toward the acid side; there are inflammatory changes in the skin, pericardium, larynx, pharynx, stomach and intestine. Toxic irritation of the nervous system is indicated by involuntary muscle spasms and sublethal tetanoid. There is a toxic impairment of erythropoiesis. The development of renal insufficiency and true uremia may be so insidious that the physician does not think of renal disease but of pulmonary or cardiac disorder. However, increased respiration the result of acidosis differs from that of cardiac or pulmonary dyspnea. There is present the characteristic lack of color of the urine, a specific gravity of about 1.010 and xanthoproteic test of Becher. It is also necessary to recognize cases

of relative renal insufficiency that are compensated by polyuria. These cases are characterized by dyspeptic manifestations, lack of appetite, aversion to meat and unquenchable thirst. The second important factor in Bright's disease, namely the increased permeability of the renal membranes, particularly of the glomeruli for albumin, becomes serious only if the loss of albumin in the urine exceeds the capacity of the liver to form blood protein. This process, which results in hypoalbuminemia, is often favored by the prescription of an unsuitable, protein deficient diet and is followed by hunger edema. In these cases of protein hunger the dropsy is of extrarenal origin; its development during nephrosis has no connection with a decrease in the renal secretion but is caused by the increased permeability of the kidney. The third factor, the disturbance of the renal or glomerular blood perfusion, is the most important since it causes most of the remote symptoms. Cardiac hypertrophy of Bright's disease develops on the basis of increased blood pressure. The disturbance in renal blood perfusion activates the chemical hematogenic mechanism, which produces pale hypertension in the form of a generalized vascular contraction, which at its height gives the impression of a general arterial ischemia. The latter is at the basis of some of the clinical symptoms which formerly were regarded as toxic or uremic, namely albuminuric retinitis, convulsive uremia, pseudo-uremia, symptoms of cerebral pressure with headache, vomiting, choked disk, amaurosis and fatigue, as well as cardiac symptoms in the form of asthma or of angiospastic coronary insufficiency. Kidney diseases in which blood perfusion is not impaired have a much better prognosis.

### Wiener klinische Wochenschrift, Vienna

53:637-656 (Aug. 9) 1940

\*Diagnosis and Treatment in Swelling of Brain. M. de Crinis.—p. 637.  
Treatment of Epidemic Meningitis with Azosulfamide. W. Maier.—p. 640.

\*Bence Jones Albuminuria. E. Dworacek.—p. 641.  
Therapeutic Experiments with Organ Specific Lipoid Extracts. A. Ringl.—p. 644.

**Swelling of Brain.**—According to de Crinis it is necessary to differentiate between swelling and edema of the brain. Swelling of the brain is an enlargement in volume which is not a direct result of hyperemia, cerebral edema or hydrocephalus. The chief difference between swelling and edema is that in swelling the water content of the brain is less and the consistency is greater than in edema. The increased volume in swelling of the brain infringes on the available space and choked disk, signs of vagal irritation (slow pulse and nausea) and headaches appear. For the necropsic diagnosis of brain swelling it is essential that the necropsy be made shortly after death, for, if considerable time elapses, brain swelling may result from the postmortem absorption of cerebrospinal fluid. The macroscopically visible signs of brain swelling are flattening of the convolutions and reduction of the cerebrospinal fluid spaces and of the subarachnoidal space; also the consistency of the brain is increased and it is comparatively dry and sticky. Brain swelling is regularly found following death during status epilepticus, status paralyticus, uremia, puerperal eclampsia, after sudden death in catatonic excitation, from electrical brain lesions and from inflammatory diseases of the brain such as encephalitis and meningitis, and from cerebral abscess. In children who died suddenly, brain swelling has been known to be the only pathologic manifestation. The author gives particular attention to brain swelling in cerebral tumors. The swelling of the brain does not parallel the size of the brain tumor. Fist-sized tumors on the frontal brain may exhibit no signs of spatial limitation, whereas small tumors, the size of a cherry, may produce pressure and sudden death. Brain swelling with the acute signs of cerebral pressure often develop after transportation of patients with cerebral trauma or tumor. Incidence and extent of brain swelling are determined by the type of tumor. Tumors with infiltrating growth such as gliomas cause swelling more readily than circumscribed tumors. Meningiomas cause brain swelling only after they have reached a certain size. Swelling of the brain is rare in the presence of angiomas. The clinical symptoms of brain swelling may be fleeting at first and they may not be limited to the immediate vicinity of the focus of the

disease but may involve distant regions. The fleeting character and the mildness reveal that they are neighborhood or distant symptoms rather than focal or nuclear symptoms. Response to treatment may likewise be of help in determining whether symptoms are caused by brain pressure or by a tumor. The author discusses measures effecting dehydration which not only reduce the pressure on the brain but also permit a conclusion regarding the cause of the swelling. Urea plays an important part in tissue metabolism and in the physicochemical condition of the tissues. The author was able to demonstrate urea in the brain tissue of patients in whom cerebral tumor or abscess, encephalitis, status epilepticus or delirium tremens had produced brain swelling. He is convinced that swelling of the brain is chiefly a physicochemical problem. The living brain contains lipoids and protein bodies which are in different states of swelling. The state of swelling is dependent on humoral, toxic and other influences. In swelling of the brain, the tendency of the colloids to absorb water is increased beyond physiologic limits. In edema of the brain the absorption tendency is reduced and water is given off. This differing physicochemical behavior of the brain colloids is due to pathologic processes some of which are still unknown.

**Bence Jones Albuminuria.**—Many investigations have been made to determine the characteristics and the origin of the Bence Jones protein of the urine of patients with multiple myeloma and of some with chronic leukemia. These studies, according to Dworacek, and those on the blood protein bodies of patients with Bence Jones albuminuria have not produced uniform results. The investigators are divided on the question whether the Bence Jones protein is of exogenic or of endogenic origin. On the basis of the extensive investigations of Magnus-Levy it is now generally assumed that the elimination of Bence Jones protein is largely dependent on the nitrogen metabolism. It is not a purely autogenous product but is influenced by various food proteins. The author reports studies on a patient with multiple myeloma. The protein was isolated from the mixed urine during a time when the patient was on a diet with a relatively restricted protein intake. The method used was that of Mainzer. It was found that the average daily elimination of Bence Jones protein was 2 Gm. The protein solution as well as the urine produced the customary precipitation expected of a Bence Jones protein body: (1) beginning flocculation at 60 C., maximal turbidity at 65 C., clearing at 80 C., complete clarification at 97 C. and precipitation on renewed cooling; (2) flocculated precipitation on addition of a 25 per cent solution of nitric acid, heat solubility; (3) precipitation with 12.5 per cent solution of hydrochloric acid and liquefaction in heat; (4) precipitation with ferricyanic acid and redissolving on heating; (5) irreversible precipitation on addition of 96 per cent alcohol and other precipitation reactions. An analysis of the purified dry substance of the isolated protein revealed that the values determined differed from those obtained by others. The author thinks that this is due to the fact that the Bence Jones protein is not a definite chemical entity but that its composition is determined by physiologic conditions and particularly by the nitrogen metabolism. Six months later, when the patient still received the same diet, the tests were repeated and practically the same results were obtained. The patient was put on a meat diet with a high protein content and after two weeks the urine was collected and Bence Jones protein was isolated again. A comparison of the values found on analysis of the Bence Jones protein obtained in the three successive examinations disclosed during the third an increase in nitrogen, tryptophan, arginine and particularly tyrosine, whereas sulfur, cystine and histidine had remained practically the same. These results make probable a dependence of the Bence Jones protein on food proteins. The author did not succeed in isolating the Bence Jones protein from the blood, but he points out that the sedimentation speed of the erythrocytes is increased in patients with multiple myeloma. Since the Bence Jones protein has the colloid character of serum albumin, he decided to investigate the dependence of the sedimentation reaction on this protein. He made the surprising discovery that the addition of a solution of Bence Jones protein to normal blood considerably retards the sedimentation speed and he thinks that the albumin character of the Bence Jones protein is responsible for this.

53:697-716 (Aug. 30) 1940

- \*Single Massive Doses in the Therapy and Prevention of Rickets. G. O. Harnapp.—p. 698.  
 Contraselection. K. Keller.—p. 701.  
 The Health Wagon (Motorized Preventive Medicine for Rural Districts). F. Hamburger.—p. 703.  
 Origin and Value of the Health Wagon. Adele Bornefeld.—p. 704.  
 Experiences with First Health Wagon in Zwettl District, Lower Danube. H. Goll.—p. 705.

**Vitamins D<sub>2</sub> and D<sub>3</sub> in Rickets.**—Harnapp found single massive doses of from 10 to 15 mg. of vitamin D<sub>2</sub>, orally administered, of sufficient concentration to effect the cure and prevention of rickets. He claims for this dosage the regeneration of even pronounced rachitic osteomalacia. Prolonged tests were made on some 100 clinically controlled inmates of a children's home. Analyses of feces showed that 93 per cent of the vitamin was retained in the body. Craniotabes generally diminished after four to five days and often ceased to be palpable from eight to ten days after the single treatment. Blood chemistry assays indicated respectively mounting phosphate or calcium levels after fourteen to twenty-four hours. Spontaneous fractures rapidly developed callus formations. Calcic regenerative processes were roentgenologically seen to occur after four days. Vitamin D<sub>2</sub> was likewise therapeutically significant in spasmodophilia and in complications with pertussis and pneumonia. Its prompt effect in general well-being was surprising. Querulous and apathetic children of preschool age suffering from severe rickets were observed several days after the vitamin was given to indulge in play and hilarity. Roentgen, blood and electrocardiographic tests failed to disclose any toxic effects of massive dosage. Experiments with vitamin D<sub>2</sub> in the prevention of rickets, carefully controlled for a sufficiently long period of time on a large number of children, indicated that 7.5 mg. was the minimum safe dose. Experiments with vitamin D<sub>3</sub>, on the other hand, seemed to show a slight superiority of this vitamin over vitamin D<sub>2</sub>, since 5 mg. of D<sub>3</sub> achieved the same prophylaxis as 7.5 mg. of D<sub>2</sub>. However, further investigations of the relative potency of D<sub>2</sub> and D<sub>3</sub> are in order. In view of the difficulty of determining the initial onset of rickets after the first six months of neonatal life, the author is of the opinion that all nurslings and infants, irrespective of their physical appearance, should be prophylactically treated with vitamin D<sub>2</sub> in the dosage indicated. He thinks that rickets could be completely abolished if this preventive measure was universally applied. To insure the child's welfare against the well known therapeutic laxness of the public when visible signs of the disease are absent, medication should be done by the physician himself.

### Zeitschrift für Urologie, Leipzig

34:249-304 (No. 6) 1940. Partial Index

- \*Experiences and Results with Endo-Urethral Resection of Prostate. A. Röbbelen.—p. 249.  
 Foundations of Pathologic Pyelogram. A. Herzog.—p. 273.  
 Early Roentgenologic Diagnosis of Renal Tuberculosis. O. Olsson.—p. 283.  
 Temporary Subcapsular Hemostasis in Nephrotomy in Situ. B. von Mezö.—p. 294.

**Endo-Urethral Resection of Prostate.**—Röbbelen points out that the enthusiasm for the endo-urethral resection of the prostate, which in some clinics led to its application in 99 per cent of the cases of hypertrophy of the prostate, has somewhat diminished in the last few years, because complications and failures were observed. Hemorrhage, rupture of the bladder, inflammation of the pelvic floor and peritonitis as immediate sequels, and infections, incontinence and rectovesical fistulas as late complications were reported. Endo-urethral interventions are often followed by a prostatitis, cystitis and great irritability of the bladder more annoying than the difficulties in micturition. A number of surgeons, however, hold a favorable opinion of the endo-urethral resection. The author discusses the indications and the results with endo-urethral electroresection for hypertrophy of the prostate on the basis of 100 electroresections and forty-one follow-up examinations in Konjetzny's clinic. For physiologic reasons he prefers the term "valve lobe" to "hypertrophy of the middle lobe." Electroresection offers the best results in the presence of valve lobes. It was employed also in hypertrophy of the lateral lobes because isolated valve lobes were seen in only 11 of the 100 cases. Hypertrophy of the lateral lobes alone, or in combination with valve lobes, existed

in 79 cases, carcinoma of the prostate in 8 and sclerosis of the sphincter in 2. One of the most serious complications in electroresection is hemorrhage. It was severe in 9 of the cases. Other complications were epididymitis in 7, injury of the urethra in 1, chills in 3 and high temperatures in 6. The mortality rate was 5 per cent. Death resulted in 1 case each from sepsis, coronary sclerosis and tabes, and in 2 cases from embolism. The after-treatment required on the average twenty-one days. At the time of discharge, 45 of the patients were free from residual urine, 44 had less than 50 cc., the remaining up to 100 cc. or more, and 2 were not improved. Of the 41 patients who were followed up from one to four years, 21 had remained free from residual urine, 12 had from 10 to 50 cc. of residual urine, 4 had from 50 to 100 cc. and the remainder had from 100 to 250 cc.; 1 had to continue the use of a permanent catheter and another had a return of retention. At the Konjetzny clinic adenoma of the prostate is enucleated by the open operation whenever possible. Endo-urethral resection is resorted to when the radical operation is no longer possible. If a correct technic is employed the endo-urethral resection gives satisfactory results with freedom from catheters and fistulas.

### Bibliotek for Læger, Copenhagen

132:213-223 (Oct.) 1940

- \*Erythrothrombomonoblastosis. K. Kjerulf-Jensen.—p. 213.

**Erythrothrombomonoblastosis.**—Kjerulf-Jensen states that while his 2 patients, women aged 60 and 65 with a history of eleven and six years' duration respectively, clearly were affected differently, the following symptoms were common to the 2: (1) initial splenomegaly (extirpation of the spleen done in both), (2) changes in the blood picture (consisting of constant thrombocytopenia, constant erythroblastemia and hypochromatic anemia, atypical or immature monocytes in peripheral blood, increased bone marrow activity seen in sternal punctate), (3) considerable increase in metabolism with sweating, tachycardia and palpitation, (4) bone atrophy (in the first case of Gaucher type). After splenectomy the second case took on a more leukemic character with more affected general condition. There was periodic marked hemorrhagic diathesis, with marked enlargement of the liver, moderate enlargement of the lymph nodes of the neck and universal osteoporosis. Since splenectomy, the first case has progressed slowly for seven years, the second more violently and rapidly for three years. The diagnosis is not certain in either case, and only knowledge of the future course and eventual biopsy and possible necropsy will definitely clarify the picture. Temporarily the cases are classified as chronic erythrothrombocytomonoblastosis, a sweeping protracted leukemia-like disorder of the hemopoietic system in which splenectomy is not assumed to have any decisive effect.

### Ugeskrift for Læger, Copenhagen

102:991-1018 (Sept. 26) 1940

- \*Diagnostic Value of Sternal Puncture: Review in Connection with Personal Investigations. H. Gormsen.—p. 991.  
 Sanatorium Treatment of Diabetes Mellitus. Agnete Bræstrup.—p. 999.  
 Some Clinical Vitamin B<sub>1</sub> Analyses by Aid of Mold Method. H. O. Bang.—p. 1000.  
 Fissure Formation in Articular Processes of Lumbar Vertebrae. V. Simonsen.—p. 1002.  
 Case of Fatal Carbon Monoxide Intoxication Due to Use of Charcoal Stove. H. Reistrup.—p. 1003.

**Diagnostic Value of Sternal Puncture.**—Gormsen emphasizes the decisive part played by sternal puncture in the diagnosis of less typical cases of pernicious anemia and of cases of aleukemic leukosis, myelomatosis, lipoidosis, tumor metastases to the bone and Boeck's sarcoid. Bacteriologic examination of the sternal punctate can also be of value, for example, in septicemia and typhoid. He reports on differential counts made in the bone marrow from thirty normal adults. Tumor cell complexes were demonstrated in the sternal punctate in 8 of 131 cases of malignant tumors (twenty-one sarcomas, one hundred and ten carcinomas). Metastases in the bone marrow were not established in any of the cases of sarcoma. Tumor cells were established in 7 of the 39 cases of cancer of the breast. In 1 case out of 5 with cancer of the prostate metastases were found in the bone marrow, and in 1 out of 5 cases of Boeck's sarcoid the characteristic granuloma was demonstrated in sections of the sternal punctate.



## Book Notices

**An Introduction to Gastro-Enterology.** By Walter C. Alvarez, Professor of Medicine, University of Minnesota, Minneapolis. Being the third edition of *The Mechanics of the Digestive Tract*. Cloth. Price, \$10. Pp. 778, with 186 illustrations. New York & London: Paul B. Hoeber, Inc., 1940.

From a booklet first published in the early 1920's as "The Mechanics of the Digestive Tract" has evolved this stately volume. It is probably the most human gastro-enterology that has been published, leaning largely toward the functional rather than the pathologic aspects of the subject. The book is one of the most readable of medical works, since its author has a well established literary style and a good journalistic sense. His discussion of peristalsis is readable beyond any similar analysis of that valuable function that is elsewhere available. Indeed, the opening chapter serves merely as an introduction to a full discussion of the mechanics of bowel activity, leading eventually to an understanding of peristalsis, belching, nausea and many another symptom generally accredited to the subject of disturbance of the stomach.

Especially interesting is the insistence of the author on correct use of terms so they will mean the same things to all scientists. This emphasis on somatics is another unusual feature for a medical work. There are chapters on chewing, swallowing, on movements of the stomach, hunger pains, vomiting, the gallbladder, the colon, constipation, and eventually an analysis of surgical procedures and medical methods of study.

Since titles such as "gastric secretion" and "pancreatic secretion" do not appear in the index and since the title of this edition has been changed to "An Introduction to Gastro-Enterology," the reviewer has conjectured that this "introduction" is a first volume to be followed in the course of time by a companion volume dealing with the secretory glands which pour their digestive juices into the gastrointestinal tract. It is hoped that this conjecture is correct, for no one is in a better position to supply both the student body and the alert scientifically minded clinician with an account of the secretory side of gastrointestinal activity.

The book is replete with fine photographs of important contributors, with excellent drawings, and with supplementary chapters on books and reading, an extensive bibliography and an index. Here obviously is a "must" book for the general practitioner as well as for the gastroenterologist.

**Psychiatric Clinics for Children with Special Reference to State Programs.** By Helen Leland Witmer, Ph.D., Research Associate, National Committee for Mental Hygiene. Cloth. Price, \$2.50. Pp. 437. New York: Commonwealth Fund; London: Oxford University Press, 1940.

This work is based on studies of child guidance clinic services made by staff members of the National Committee for Mental Hygiene. It provides information for those interested in the extension of psychiatric clinic service to children, particularly in nonmetropolitan areas. The author discusses the theoretical and historical background of clinical child psychiatry and the evolution of psychiatric clinics for children. She particularly emphasizes the influence of the theories and activities of Adolph Meyer, "who exerted the greatest influence on the development of child psychiatry under state auspices." The more specific contributions of Freudian psychology to American child psychiatry are conservatively and constructively presented.

The second general section is a survey of state financed psychiatric clinics for children. The author finds many limitations in the programs possible under state hospital auspices and concludes that "there was little evidence that state hospitals had been much influenced by child guidance theory and practices." She describes in detail the work and services of the Northern New Jersey Clinics and of the Worcester Child Guidance Clinic, two services officially under state hospital auspices and clinics conducted by psychopathic hospitals, that is hospitals set up to observe and temporarily care for incipient and transitory mental disturbances (the Boston Psychopathic Hospital and the Colorado Psychopathic Hospital). Many factors militate against rapid progress toward the goal of develop-

ing psychiatric services extensively available to the children of rural communities. Great difficulties are encountered in having the diagnostic services of the clinics reflected in appropriate treatment steps. Limitations in local professional personnel and resources are among the handicaps.

The third section of the book, on principles for future programs, is a serious attempt by the author to evaluate the experience made available by the survey and to define the objectives of the psychiatric clinics for children. Evidence is presented indicating that clinics designed to offer psychiatric assistance for mentally retarded children can be expected to be helpful in furthering the adjustment of these children.

In a chapter on modern child guidance as a means of promoting mental health, Dr. Witmer has attempted to review psychiatric principles basic to child guidance, to contrast child guidance with other forms of child psychiatry and to outline differences in goals and methods of treatment in child guidance clinics. This is a chapter worth careful reading, although it tends to be somewhat more an interpretation of the role of the psychiatric social worker than is explicitly stated as its objective. The book concludes with a chapter on the planning of the psychiatric service for small communities.

This is a unique work, which should be consulted by all who are interested in the organization and establishment of psychiatric services for children. It is strange, however, that the author, in her discussion of the background and evolution of child guidance clinics, could have failed to make a single reference to an individual whose personal influence, practical insights and amazing organizing ability accomplished at least as much for the development of child guidance in the United States as has any other individual, namely Herman M. Adler. To be sure, the services he instituted or enriched are discussed, but the failure to include an evaluation of his influence in bringing about that synthesis of the efforts of psychiatrist, psychologist and social worker reflected in the present day organization and spirit of the Child Guidance Center is a perhaps minor but noteworthy lapse.

**Atlas of Cardio-roentgenology.** By Hugo Roesler, M.D., F.A.C.P., Associate Professor of Roentgenology, Temple University School of Medicine, Philadelphia. Cloth. Price, \$8.50. Pp. 124, with 166 illustrations. Springfield, Illinois & Baltimore: Charles C. Thomas, 1940.

This atlas of cardio-roentgenology by the author of *Clinical Roentgenology* and *System*, consists of sixty case reports. These reports contain a brief summary of the history, physical examination, laboratory observations and necropsy. Most of the cases are illustrated with roentgenograms in two or more positions, electrocardiograms, photomicrographs of histologic sections, and photographs of the heart made by a new method which utilizes longitudinal or window sections of the hardened specimen. The faithful reproduction of many beautiful photographs of the heart is an important feature of the work.

The first ten case reports are intended to familiarize the reader with the normal roentgen appearance of the heart. The next fifty cases deal with many common and rare diseases. Some of the common diseases described are cardiac failure, pulmonary edema, hypertensive arteriosclerotic heart disease, postural circulatory deficiency, cardiac enlargement in anemia, influence of scoliosis and funnel chest on the appearance of the cardiac silhouette, evaluation of the heart size in emphysema, elongation and dilatation of the aorta due to syphilis, aortic aneurysm, myocardial infarction, and rheumatic heart disease with mitral stenosis and other valvular lesions. Among the less common conditions described are cardiac aneurysm, metastatic cardiac tumor, intracardiac calcification associated with hyperparathyroidism, calcareous pericardial disease with cardiac compression and pneumomediastinum. Among the cases of congenital cardiac malformations are interatrial septum defect, aneurysmal dilatation of the pulmonary artery, congenital pulmonary stenosis, right sided aortic arch, and transposition of the great vessels.

Case 40, for example, contains two roentgenograms, two large photographs of the anterior and posterior aspects of the whole heart and photographs of eight sections of the heart. Case 49 is illustrated with four roentgenograms, one electrocardiogram, three large photographs of the heart and one photomicrograph.

A type page of 45 by 63 picas (about  $7\frac{1}{2}$  by  $10\frac{1}{2}$  inches) permits the use of large figures which show all essential details. The book contains a detailed table of contents but no index.

This authoritative work is a fine example of the printer's art and should be useful to roentgenologists, cardiologists and all others who are interested in diseases of the heart.

**Clinical Pathology and Treatment of the Dental Pulp and Periodontal Tissues.** By Edgar D. Coolidge, B.S., M.S., D.D.S., Professor of Therapeutics, Preventive Dentistry and Oral Hygiene, Chicago College of Dental Surgery, School of Dentistry, Loyola University, Chicago. Cloth. Price, \$6.50. Pp. 461, with 289 illustrations. Philadelphia: Lea & Febiger, 1939.

This is an excellent addition to the text and reference literature on the subject. The preface says "This book is the outgrowth of many years of teaching and clinical experience in the treatment of the pulp and periodontal tissues. It represents the author's study, research, observation and deductions over a period of more than twenty-five years." Among the topics treated in the twenty chapters are dental pain and its diagnosis, treatment of the dental pulp in which vitality should be preserved, treatment of vital pulps that should be removed, removal of the pulp and preparation of root canals for filling, anatomy of root canals with relation to pulp removal and root canal fillings, principles and technic of filling root canals, healing and repair after pulp removal and root canal filling, treatment of infected pulps and pulpless teeth, treatment of teeth with inflammatory disturbances of the apical periodontal tissues, gingivitis associated with systemic disturbances, functional response to excessive or abnormal occlusal stress, treatment of functional and traumatic injuries in the periodontal tissues and treatment of suppurating periodontal pockets. The author attempts to relate treatment to tissue reaction and the biologic principles involved. He discusses all the accepted methods and gives the reasoning on which the advocates of these methods base their program. The attention of the medical profession is especially called to chapters IX, X and XI. A careful study of these chapters would help to clear up much of the misunderstanding that has existed with reference to the pulpless tooth. The work is profusely illustrated with a large number of photomicrographs. As a specimen of book making it is fully up to the high standards of the publishers. It will be a valuable student textbook and of unusual interest to the clinician.

**Die Methoden der Fermentforschung.** Unter Mitarbeit von Fachge nossen. Herausgegeben von Prof. Dr. Eugen Bamann und Prof. Dr. Karl Myrback. Lieferung I. Boards. Price, 18 marks. Pp. 172, with 2 illustrations. Leipzig: Georg Thieme, 1940.

This is the first published section of a projected reference work on enzyme research. When completed it will be about 3,500 pages long and will cover the chemistry and preparation of substrates, the methods of following enzyme activity, the detailed description of enzymes and the applications, industrial and clinical, of enzyme chemistry. The present section deals with the preparation, properties and mode of use of the following classes of substrates: the glycerides, acetylcholine, the tannins, chlorophyll, phosphoric esters, phosphatides, sulfuric acid esters, hexoses and glycosides. The treatment is detailed, thorough and systematic. If the work as a whole keeps to the standard set by the present section, the handbook will be indispensable to workers in the field of enzyme chemistry. The American contributors will include R. S. Anderson, M. L. Anson, E. N. Harvey, Moses Kunitz, J. H. Northrop and J. B. Sumner.

**The Histamine and Insulin Treatment of Schizophrenia and Other Mental Diseases.** By Horace Hill, M.R.C.P., Medical Superintendent, Laverstock House Mental Home, Salisbury. Cloth. Price, \$1.75. Pp. 132. Baltimore: William Wood & Company, 1940.

The author states that histamine is present not only in insulin shock but in every variety of shock and, further, that evidence goes to show that in the cases of induced fits (i. e. convulsion therapy) the thing of essential importance is not the actual fit but the histamine formed. These statements, mainly the first parts of them, one can hardly argue away. The originators of the insulin and convulsion treatments themselves never believed or stated that the curative agent of the so-called shock therapies is the shock itself. On the contrary, they always emphasized that the biochemical changes connected with the shock are of

primary importance. What these unknown factors are, the mutual and forced work of innumerable researches here and abroad have not determined for the time being. Unfortunately the flat assumptions of the author cannot replace meticulous research work. Not regarding, however, the weakness of its theoretical bases, the method, being presumably without dangers, is worthy of a trial. The treatment comprises a series of three or four treatments each consisting of from fifteen to twenty injections of 5 to 10 units of insulin combined with 0.2 to 2.0 mg. of histamine. The injections may be given daily or, better, every second day. The reactions of the patients are slight as compared to the shock treatments; however, the treatment is contraindicated in cases of asthma, increased blood pressure, heart and liver disease, thickened and stiff arteries and pregnancy. The author claims that his method has more effect in chronic cases than other methods. In addition the book contains thirty case histories which are sometimes convincing, though the classification of the results as "well," "improved" and "indefinite" sounds itself rather indefinite.

**Veterinary Bacteriology.** By I. A. Merchant, D.V.M., Ph.D., C.P.H., Associate Professor of Veterinary Bacteriology and Hygiene, Iowa State College, Ames. Cloth. Price, \$7. Pp. 628, with 135 illustrations. Ames: Iowa State College Press, 1940.

The author has arranged a curriculum for undergraduate students of veterinary medicine covering the more common pathogenic micro-organisms affecting domestic animals. On the valid and customary ground that bacteriology has a broader definition than the word indicates, molds, yeasts, filtrable viruses and bacteriophage are included. Protozoa, however, are left for the parasitologist. The opening chapter is a brief but quite accurate account of the historical events which led to the present conception of micropathology. Infection, immunity, anaphylaxis and serologic tests are outlined. The technics and methods related are those commonly employed in the teaching of elementary bacteriology. The terminology, classification of bacteria and the descriptive material conform to modern usage. The more important species of *Salmonella* affecting man and animals are singled out for particular attention. The species of this genus are well chosen and well described as to their history, their hygienic significance and the laboratory methods now employed in classifying them. The chapter on filtrable viruses lacks some of the newer knowledge of the nature of viruses and virus infections but is nevertheless a reminder that veterinarians are entitled to a great deal of credit for having conquered by vaccination such grave virus infections as hog cholera, canine distemper, avian variola, rinderpest, and equine encephalomyelitis. The fault of this book is the brevity of the contents, owing to the usual attempt to cover everything related to medical bacteriology in a too small volume.

**Surgical Nursing.** By E. L. Eliason, A.B., M.D., Sc.D., Surgeon, University of Pennsylvania, Philadelphia General and Presbyterian Hospitals, Philadelphia, L. Kraefer Ferguson, A.B., M.D., F.A.C.S., Assistant Professor, University of Pennsylvania Medical School, Philadelphia, and Evelyn M. Farrand, B.N., B.S., Instructor in Nursing Arts and Surgical Nursing, University of Pennsylvania Training School for Nurses. Sixth edition. Cloth. Price, \$3. Pp. 673, with 245 illustrations. Philadelphia, Montreal & London: J. B. Lippincott Company, 1940.

There is always a good reason why some books become popular and require a number of editions at frequent intervals. In this case the reason is evident. This book on surgical nursing is everything a textbook on this subject should be. In clear and simple language it covers the entire field of surgery briefly but adequately enough to give the student nurse an ample insight into the subject. In addition there are clear, concise descriptions not only of what to do and how to carry out each procedure but also why it should be carried out in a certain way. For this reason there are sections on anatomy, physiology and microbiology as applied to the surgical principles involved in nursing care. The book is accurate and abreast of the times. It includes discussions of the Wangenstein suction apparatus, the use of the Miller-Abbott tube, chemotherapy and the newer drugs and anesthetics. The large number of well prepared photographs, diagrams and drawings illustrating individual points of technic vividly enhance the value of the text. Altogether this book is what it was intended to be, a textbook on surgical nursing, and it is an excellent one.

## Queries and Minor Notes

THE ANSWERS HERE PUBLISHED HAVE BEEN PREPARED BY COMPETENT AUTHORITIES. THEY DO NOT, HOWEVER, REPRESENT THE OPINIONS OF ANY OFFICIAL BODIES UNLESS SPECIFICALLY STATED IN THE REPLY. ANONYMOUS COMMUNICATIONS AND QUERIES ON POSTAL CARDS WILL NOT BE NOTICED. EVERY LETTER MUST CONTAIN THE WRITER'S NAME AND ADDRESS, BUT THESE WILL BE OMITTED ON REQUEST.

### CEREBRAL VASCULAR LESIONS AFTER CARBON MONOXIDE POISONING

**To the Editor:**—A white man aged 37, a laborer, was treated on Nov. 8, 1940 in our hospital by another physician for two days for carbon monoxide poisoning, apparently making a good recovery. On November 27, while working as a laborer, he had a sudden severe pain in his head and was brought to the hospital for observation. Pain in the head was accompanied by vomiting. Blood cell counts were as follows: November 27, erythrocytes 4,600,000, leukocytes 6,250. On Dec. 7, 1940 he was normal apparently in every respect. Blood cell counts were normal. His discharge was considered. About 3 a. m. on December 8 he had more cerebral pain with vomiting and lapsed into unconsciousness. The pulse was about 48, respiratory rate 10, blood pressure 94 systolic and 60 diastolic. Spinal puncture revealed bloody spinal fluid under considerable pressure. In spite of all treatment, including oxygen, he died at 4:45 p. m. There was no history of injury to the head, and the question has arisen as to whether carbon monoxide poisoning, which occurred about a month ago, could have caused cerebral hemorrhage and death.

W. H. Paige, M.D., Brownwood, Texas.

**ANSWER:**—This question cannot be satisfactorily answered in view of the fact that no real data are given covering the degree of asphyxia experienced by the patient when poisoned on or about November 8. Since he was hospitalized over several days presumably his asphyxia was great. The following material from Drinker's book (Drinker, C. K.: Carbon Monoxide Asphyxia, New York, Oxford University Press, 1938) on carbon monoxide poisoning seems pertinent:

"Semerak and Bacon (1930) have written an excellent summary of the literature on vascular lesions not only in the brain but in the body generally. There is no doubt that fatty, hyaline and other retrogressive changes of vessel walls, particularly of the small arterioles, may follow gas poisoning of severe grade and that the actual duration of asphyxia necessary to produce such changes may be as short as twenty minutes. A very different question arises in connection with the possible causation or intensification of arteriosclerosis as a result of chronic or of relatively mild single exposures. In my opinion there are no reliable pathologic data to support such contentions, though the issue has been raised medicolegally in the past and will undoubtedly be raised again.

"The effects of carbon monoxide on blood vessels are undoubtedly more severe in old people with a certain degree of antecedent arteriosclerosis than they are in young persons with normal vessels. As a result, an old person may emerge from a severe gassing with a hemiplegia, or may develop such a condition suddenly a week to three weeks after the accident."

### WATER SOLUBLE BISMUTH FOR TUBERCULOSIS

**To the Editor:**—I have received reports of the treatment of pulmonary tuberculosis by the intravenous injection of water soluble bismuth. Will you give me the status and your opinion as to this form of therapy.

J. D. Riley, M.D., State Sanatorium, Ark.

**ANSWER:**—Bismuth compounds have been used in medicine since about 1785. The insoluble salts of bismuth have been employed extensively on inflamed surfaces, as they have a mechanical or protective action. When applied to wounds or to inflamed mucous surfaces they dry the secretions and form a protective covering. A small amount of bismuth goes into solution and has a mild antiseptic action. The insoluble compounds are opaque to the roentgen rays and therefore have been used in outlining the shape of the stomach and intestine. The soluble bismuth salts do not possess the soothing qualities of those which are insoluble and therefore it is irrational to employ them on inflamed surfaces, including mucous membranes.

During this century it has been found that when aqueous or oil solutions of bismuth are administered intramuscularly in small doses they have a beneficial effect in syphilis by checking and suppressing the infection. The best effects are obtained when repeated doses are injected into muscle periodically, from which it is slowly absorbed and distributed to various parts of the body. Indeed, intramuscular administration is the only safe method of introducing enough bismuth to be effective. Even when injected in this manner, watery solutions often result in considerable pain, swelling and induration, which may persist

for several days. As bismuth is absorbed, it is distributed throughout the body but in varying concentrations in different parts. The total accumulated bismuth has been found in animal tissues to be approximately 40 per cent in the kidneys, 19 per cent in the bones, 13 per cent in the liver, 8 to 10 per cent in the muscles, 7 to 8 per cent in the skin, 2.5 per cent in the lungs and 7 per cent in all the other tissues. Doses of bismuth as large as those introduced intramuscularly when injected intravenously are dangerous and may be fatal because of the tendency of bismuth to form insoluble compounds with resulting flocculation shock. There is an immediate fall of blood pressure. If this does not result fatally there is a fairly prompt recovery of normal pressure. This action has been determined to be due to disturbed conduction and heart block.

Bismuth in the alimentary canal precipitates hydrogen sulfide and when introduced into the blood stream because of the hydrogen sulfide, which is always present in the large intestine, this precipitation may occur in the vessels of the large bowel with resulting capillary embolism and ulceration, as indicated by pain, diarrhea, vomiting and other symptoms of colitis. Thus, the effects of bismuth on the animal and human body are reasonably well known.

Rénon (*Bull. et mém. Soc. méd. d. hôp. de Paris* 44:602, 1920) states that more than twenty salts of rare earths and other elements inhibit the growth of tubercle bacilli in vitro. This group includes bismuth, gold and silver but, unfortunately, much work done since this report has shown that not one of these substances, or any other, has been found to cure tuberculosis either in man or in experimental animals. Such preparations do not reach the tubercle bacilli in sufficient concentration to have enough effect to justify their administration nor do they cause fibrosis to a sufficient degree to heal tuberculous lesions. Therefore there is no evidence that the intravenous administration of water soluble bismuth in dosage of any size has a significant effect on tubercle bacilli or the lesions they produce in the human body. Indeed, bismuth introduced directly into the blood stream is actually capable of doing harm.

### TRICHOMONAS INFECTION OF BLADDER

**To the Editor:**—A white woman aged 47 had a *Trichomonas vaginalis* infection of the vagina and bladder. I have been treating the vaginal infection with florquin tablets, vinegar douches and silver picrate suppositories. Smears from the vagina are now negative and there do not seem to be any signs of vaginal irritation. I have been treating the infection of the bladder by instillations of 0.5 per cent silver picrate solution into the bladder daily and the use of sulfanilamide, sulfathiazole and mandelic acid by mouth. Instillation of silver picrate solution will apparently clear up the infection of the bladder as long as I continue to use it every day. However, on discontinuing treatment, within four or five days' time I find in the catheterized specimen of urine from eight to ten *Trichomonas* organisms per high power field. I would appreciate any suggestions you may have with regard to treatment.

M.D., Mississippi.

**ANSWER:**—The first case of invasion of the bladder by *Trichomonas vaginalis* was reported by Marchand (*Zentralbl. f. Gynäk.* 15:709, 1894). Following this a number of single case reports appeared, giving the impression that the occurrence is rare. However, Heckel (*J. Urol.* 35:520 [May] 1936) reported a series of 43 cases, and Nitschke (*West. J. Surg.* 45:278 [May] 1937) reported 13 cases. The latter author mentions that Zenner found *Trichomonas vaginalis* in the urine of 6 women in a series of 132 cases of *Trichomonas vaginitis* infection. In this series, 36 women complained of urinary symptoms. Some authors maintain that there is a typical change in the bladder mucosa which is characteristic of a *Trichomonas* infection. Allen (*Ann. J. Surg.* 33:523 [Sept.] 1936) says "The mucous membrane change is usually limited to the urethra or the trigon of the bladder. A fluffy, edematous, almost leukoplakic looking area surrounded by or containing within its borders petechial-like spots similar to those found in the vaginal mucous membrane help identify the lesion at once." Nitschke denies that there is a pathognomonic cystoscopic picture.

In at least one case (Visser, J. W.: Vesical Infection with *Trichomonas Vaginalis*, *THE JOURNAL*, June 22, 1929, p. 2098) not only was the bladder involved but also probably the kidney. The most likely avenue of infection of the urinary tract is the urethra. In some cases the bladder infection is so severe that relief is sought only because of bladder disturbances and not because of a vaginal discharge. In many cases of bladder involvement in cases of *Trichomonas vaginalis* infection the organism cannot be found in the urine.

Various forms of therapy have been recommended. In Visser's case the condition rapidly improved after vesical and pelvic lavage with mercurochrome. Bladder irrigations with boric acid solution were followed by instillation of ½ ounce (15 cc.) of mercurochrome solution every day for a few days, then at three



